THE UNIVERSITY OF ALBERTA

I. PREPARATION AND REACTION OF TERMINAL ENOL BORINATES.

II. A NEW APPROACH TO OCTALONE SYNTHESIS

by

© ABRAHAM BENDERLY

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

SPRING, 1976

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled:

I. PREPARATION AND REACTION OF TERMINAL ENOL BORINATES.

II. A NEW APPROACH TO OCTALONE SYNTHESIS.

submitted by ABRAHAM BENDERLY in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

John Hooz
Supervisor

Jos. J. Tabata

W. F. Tyler

M. J. Robins

Ed. Krauss

Date Jan. 9, 1976

Terry Wiles
External Examiner

TO ESSIE and GILI

ABSTRACT

The regiospecific construction of terminal enol borinates was investigated. It was found that the reaction of dicyclohexylborane with 2-diazoketones resulted in terminal enol borinates. These intermediates were successfully employed in the regiospecific synthesis of terminal Mannich bases.

The "oxo-butyl" equivalent, γ-phenyl(n-butyl)thiocrotyl chloride was prepared in three facile steps from ethyl acetoacetate. The alkylation reaction of this halide with several regiospecifically generated enolates was studied. It was found that lithium enolates of cyclohexanones in DME were successfully alkylated in the presence of catalytic amount of lithium iodide. The hydrolysis reaction of the resulting γ-phenyl(n-butyl)thiocrotyl cyclohexanone derivatives was studied. It was found that titanium tetrachloride in acetic acid promoted the hydrolysis-cyclization of these compounds to the corresponding octalones.

ACKNOWLEDGEMENTS

The author wishes to thank Messrs. R. Swindlehurst and G. Bigam and their staffs for recording of the infrared and nmr spectra, Dr. A. Hogg, Mr. A. Budd, and the staff for running the mass spectra, and Mrs. D. Mahlow and Mrs. A. Dunn for determining the microanalyses.

Many thanks are due to the members of the lab for hours of helpful discussion and constructive criticism, in particular to Drs. J.G. Calzada, R.D. Mortimer, and M. MacCoss.

The author should like to express his appreciation for the interest, assistance and concern of Dr. J. Hooz, his research director.

TABLE OF CONTENTS

		Page
Abstract		v
Acknowledgements		vi
List of Tables		viii
CHAPTER		
I	PREPARATION AND REACTION OF TERMINAL ENOL BORINATES	
	Introduction	1
	Results and Discussion	13
	Experimental	28
II	A NEW APPROACH TO OCTALONE SYNTHESIS	
	Introduction	39
	Results and Discussion	53
	Preparation of γ-phenyl(n-butyl)thiocrotyl chloride	53
	A Study on the alkylation of cyclohexanones with γ-phenyl(n-butyl)thiocrotyl chloride	66
	A study on the hydrolysis of 2-[γ-phenyl-(n-butyl)thiocrotyl]cyclohexanone derivatives	76
	Experimental	97
	References	127

LIST OF TABLES

Table		Page
I	Reaction of BH_3.THF with α-diazoketones	15
II	Reaction of diazoketones with dicyclohexylborane and disiamylborane	21
III	Deuterium Incorporation of methyl alkyl ketones	24
IV	Formation of Mannich Bases by Reaction of Dimethyl(methylene)ammonium iodide with Terminal Enol Borinates	26
V	Preparation of β-alkyl(phenyl)thio-α,β-ethylenic esters	57
VI	Reduction of Ethyl β-butyl(phenyl)thiocrotonates	61
VII	The alkylation of 2,6-dimethylcyclohexanone with γ-phenyl(n-butyl)thiocrotyl chloride	69
VIII	Preparation of 2-[γ-phenylthiocrotyl]cyclohexanone	72
IX	Hydrolysis of 2,6-dimethyl-6-[γ-phenyl(n-butyl)-thiocrotyl]cyclohexanone with titanium tetrachloride in acetic acid	85
X	The reaction of 2-[γ-phenyl(n-butyl)thiocrotyl]-cyclohexanone with titanium tetrachloride	94

PREPARATION AND REACTIONS OF TERMINAL ENOL BORINATES

INTRODUCTION

Mannich bases, β-aminoketones, form an important class of organic compounds. They are mainly employed as synthetic intermediates, in which the amino function is subsequently replaced by a different group.[1,2,3,4] For examole, certain Mannich bases can undergo a reaction with nucleophile[3] such as CN^- or R_2NH to afford substitution products (eq. 1).

$$C_6H_5COCH_2CH_2\overset{\oplus}{N}H(CH_3)_2\overset{\ominus}{Cl} \xrightarrow{KCN} C_6H_5COCH_2CH_2C{\equiv}N \quad (67\%) \qquad (1)$$

A useful procedure to obtain α,β-unsaturated ketones involves the elimination of the amino function either from β-aminoketone 2, or from the corresponding quaternary ammonium salt 3 as illustrated by equation 2.

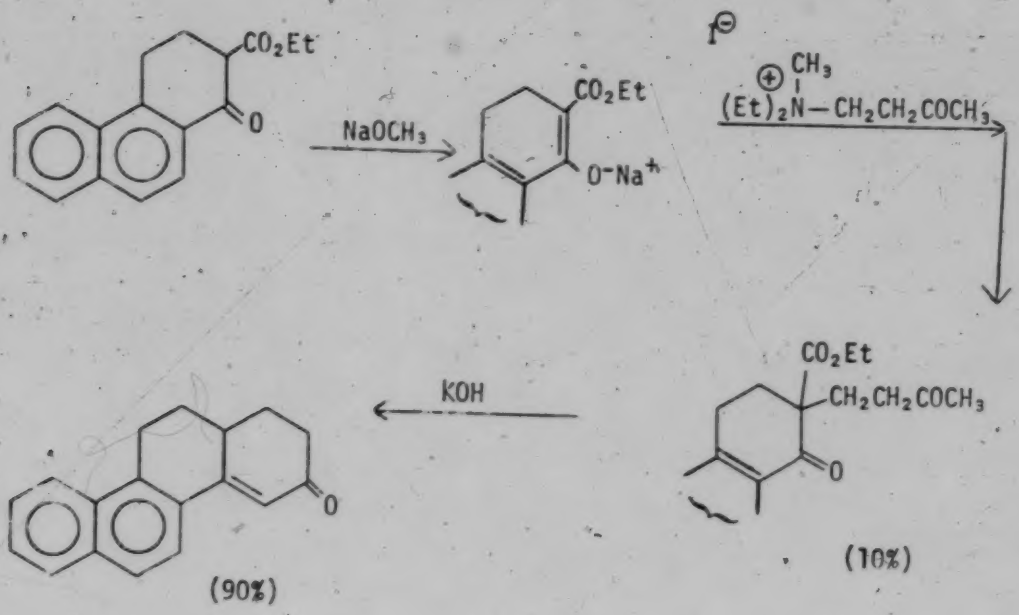
$$C_6H_5COCH_2CH_2CH_3 + (CH_2O)_3 + (CH_3)_2\overset{\oplus}{N}H_2\overset{\ominus}{Cl} \rightarrow C_6H_5COCH(Et)CH_2\overset{\oplus}{N}H(CH_3)_2\overset{\ominus}{Cl} \quad (\underline{2})$$

$$\underline{2} \xrightarrow{\text{1. base; 2. } CH_3I} C_6H_5COCH(Et)-CH_2\overset{\oplus}{N}(CH_3)_3I^- \xrightarrow[\text{distil.}]{\text{steam}} C_6H_5CO-C(Et)=CH_2 \qquad (2)$$

$$\underline{2} \xrightarrow{\text{base}} C_6H_5CO-C(Et)=CH_2$$

One of the most important uses of Mannich bases is the Robinson annelation reaction[7-25] in which enolates of fairly acidic ketones (e.g. β-ketoesters) can be alkylated under mild reaction conditions.

Subsequent cyclization of the Michael adduct comprises an important step in the synthesis of numerous natural products. (Equation 3).



(3)

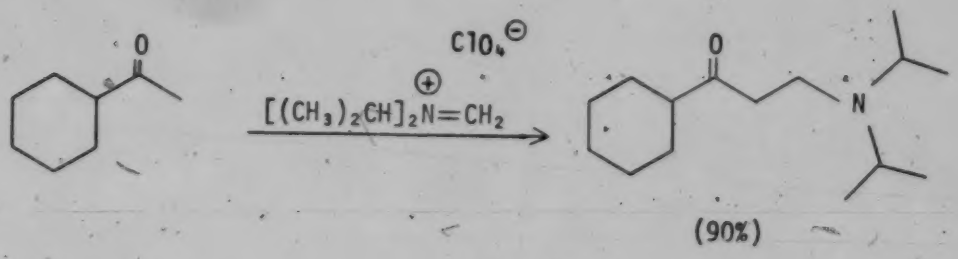
However, ketones which are not easily enolized[3,8,17] (e.g. methylcyclohexanone), unlike the previous case, give lower yields of products. The reason for these results and an extensive discussion of the Robinson annelation reaction is reserved for the second part of the thesis.

The Mannich reaction, like many other alkylation and aldol type condensation reactions, is not a regiospecific process. Of course this does not represent a problem in the alkylation of symmetrical ketones or of ketones that undergo enolization in one direction only (eq. 1). However, the alkylation of unsymmetrical ketones which can form structurally isomeric enolates (or enols) results in a mixture of products. In addition to lowering the yield of the desired alkylate, a (tedious) separation procedure is required to fractionate isomers. Generally, the major product of alkylation or condensation reactions

involving unsymmetrical ketones is that which corresponds to substitution at the thermodynamically more stable enol.[26,27,28] For example, Mannich condensation on methyl isopropyl ketone[26] resulted in two products of which the major was derived from the more highly substituted (i.e. more stable) enol (eq. 4).

$$(CH_3)_2CHCOCH_3 + (CH_2O)_3 + (CH_3)_2\overset{\oplus}{N}H_2\overset{\ominus}{Cl} \longrightarrow \underset{(76\%)}{CH_3-\overset{O}{\overset{\|}{C}}-\overset{CH_3}{\overset{|}{C}}(CH_3)-CH_2-N(CH_3)_2} + \underset{(22\%)}{(CH_3)_2CHCOCH_2CH_2N(CH_3)_2} \quad (4)$$

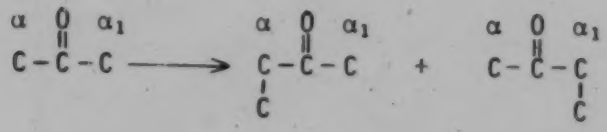
However, there are a few examples in which unsymmetrical ketones form Mannich bases corresponding to the less substituted enol[28,29] (eq. 5). In such cases, it appears likely that the reaction product is strongly influenced by steric factors. Under equilibrium conditions (long reaction time and high temperature), the product which would result from attack at the more highly substituted enol is destabilized by steric interactions. As a result, it reverts to starting material, and eventually reacts at the less hindered site.



(5)

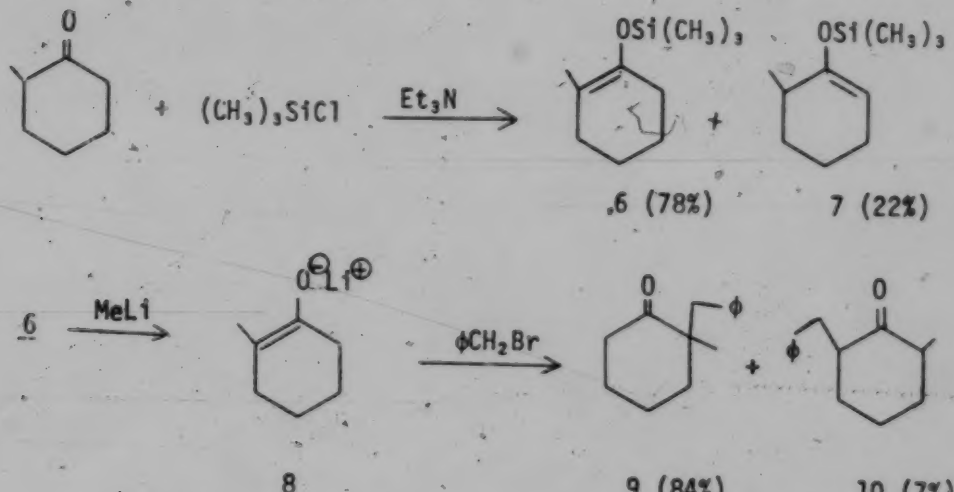
(90%)

In the past two decades various synthetic methods have been developed (such as enamines,[30] trimethylsilyl enol ethers,[31,32] enol acetates[23,33]) to alkylate selectively one of the two α-positions of unsymmetrical ketones (eq. 6).



4 5 (6)

In general, this method necessitates the specific formation of one of two possible enol derivatives. These in turn are converted, under kinetic control, to the corresponding metal enolates. As a result, unless a dominating factor such as steric interaction or thermodynamic control influence this process, an isomeric mixture of derivatives (and products) may be obtained as well (eq. 7).



6 (78%) 7 (22%)

6 → 8 → 9 (84%) 10 (7%) (7)

Clearly the above approach may be considerably improved if a synthetic method is developed which would: (a) enable the regiospecific construction of an enol derivative (uncontaminated with its structural isomer),

and (b) permit alkylation of this enol selectively without first transforming it into the metal enolate as in the above example (eq. 7). These factors have been considered by Hooz and Bridson[34,35] in their development of a new solution to the problem. Their approach is based on the reaction of organoboranes with α-diazo compounds[36] (eq. 8). This

$$R_3B + N_2CHZ \longrightarrow R\text{-}CH_2Z$$

$$Z = CO_2Et,\ CN,\ CHO,\ COR^1 \qquad (8)$$

reaction is believed[36] to proceed by an initial coordination step of the borane with the diazo compound, followed by concerted migration of the alkyl group with displacement of nitrogen (eq. 9).

$$R_3B + \overset{\oplus}{N_2}\overset{\ominus}{C}HCO_2Et \longrightarrow R_3\overset{\ominus}{B}-\underset{\displaystyle \overset{\oplus}{N_2}}{\underset{|}{CH}}-CO_2Et$$

$$R_2\overset{\ominus}{B}(R)-\underset{\displaystyle \overset{\oplus}{N_2}}{\underset{|}{CH}}-CO_2Et \xrightarrow{-N_2} R_2B-\underset{R}{\underset{|}{CH}}-CO_2Et \qquad (9)$$

When these reactions were carried out in the presence of D_2O[54] the corresponding α-deuterio esters and ketones were obtained essentially in quantitative yield (eq. 10a).

$$(C_6H_{13})_3B + N_2CHCOCH_3 \xrightarrow{D_2O} n\text{-}C_6H_{13}\underset{D}{\underset{|}{CH}}COCH_3 \qquad (10a)$$

This route was further extended for the synthesis of dideuteriomethylene ketones and α,α-dideuteroesters. For example, treatment of a mixture of trihexylborane and deuterium oxide with diazoacetone-d, gave 3,3-dideuterio-2-nonanone in virtually quantitative yield (eq. 10b).

$$(C_6H_{13})_3B + N_2CHDCOCH_3 \xrightarrow{D_2O} n\text{-}C_6H_{13}CD_2COCH_3 \qquad (10b)$$

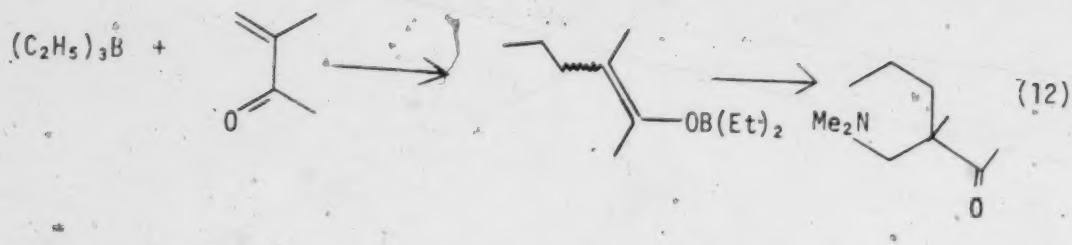
These results can be rationalized by the regiospecific formation of intermediates, presumably enol borinates, which can readily be cleaved by water to yield the corresponding alkylated carbonyl derivatives. Indeed, Pasto and Wojtkowski[37] found that the initial intermediate 11 could not be obtained from the reaction of an α-diazoester and trialkylborane, but rather the rearranged product, an enol borinate 12, was isolated and characterized.

11 12

Subsequently, Hooz and Bridson[34,35] studied the regiospecific alkylation (and bromination) of enol borinates, and found that the "Mannich reagent", dimethyl(methylene)ammonium iodide,[38] afforded excellent yields of β-dimethylamino ketones (eq. 11).

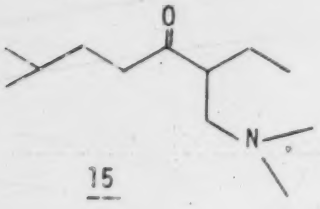
13 14 (11)

Under the mild experimental conditions employed, the positional isomer was not observed. The necessary enol borinate need not be isolated since THF solutions of these intermediates are easily and unambiguously obtained either by the reaction of trialkylboranes with α-diazoketones[36,37] (eq. 8), or by "conjugate addition" of organoboranes to a variety of α,β-unsaturated ketones and aldehydes[39] (eq. 12). Thus, this simple one flask method efficiently permits the

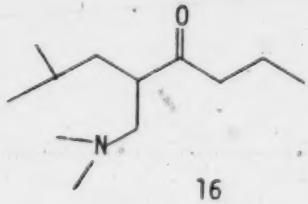


(12)

regiospecific construction of certain Mannich bases, uncomplicated by problems associated with the original Mannich reactions. By a similar approach, the "isomeric set" of Mannich bases 15 and 16 were synthesized, thus demonstrating the versatility of this method above



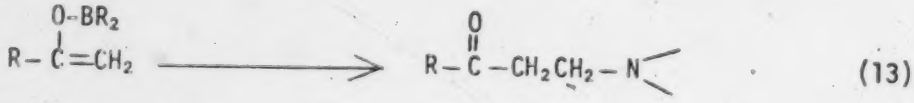
15



16

the traditional Mannich condensation reaction (which is incapable of constructing this set selectively).

It became apparent at this point that this methodology has left out an important class of Mannich bases 18, namely, the terminal Mannich bases of alkyl methyl ketones (eq. 13). To obtain this set of compounds

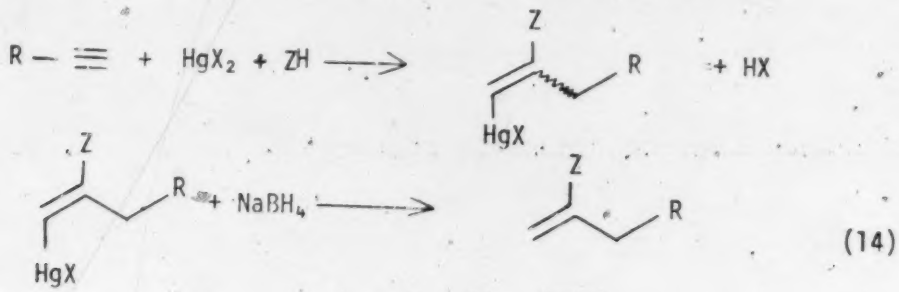


(13)

17 18

one has first to generate the terminal enol borinate 17. However, this intermediate cannot be obtained by either of the two routes described above, as an alkyl group is transferred during the reaction, resulting in the formation of an internal enol borinate 14.

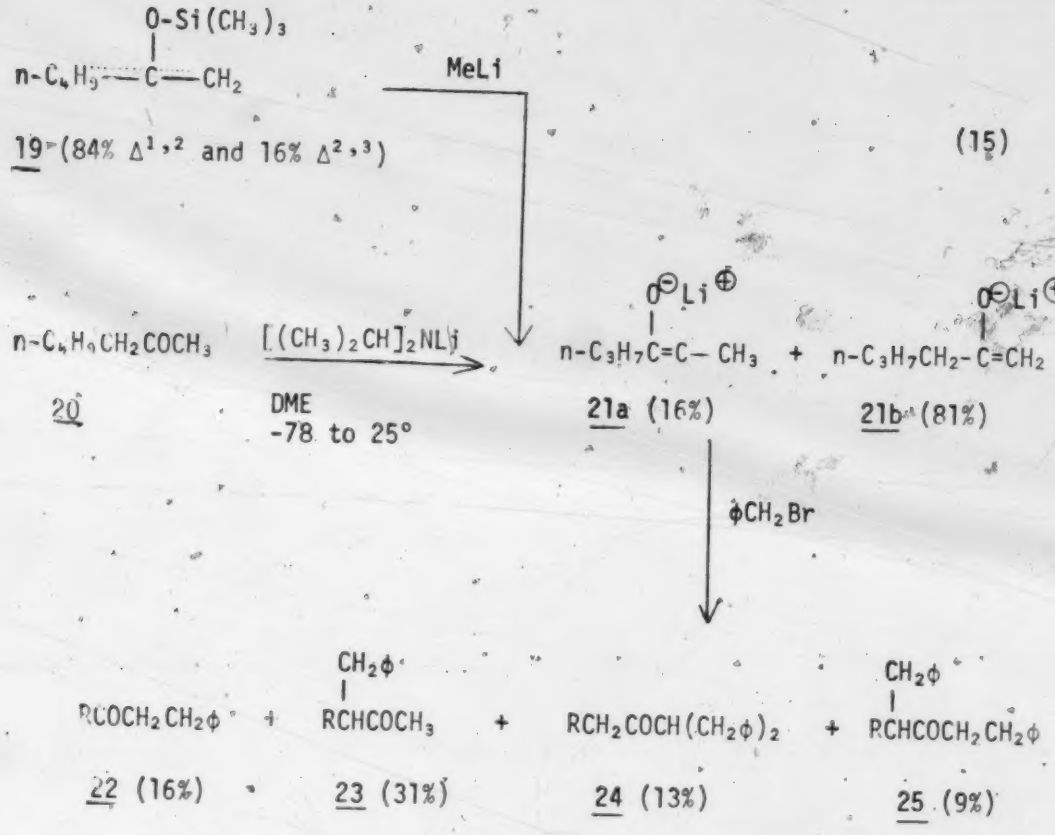
Terminal enol borinates are potentially important intermediates, especially when one considers that enol derivatives (such as enol acetates, trimethylsilyl enol ethers, etc.) having a terminal double bond are not easily accessible. An interesting indirect synthetic approach has recently been reported by Hudrlik and Hudrlik[40] who investigated the solvomercuration reactions of terminal acetylenes as a route to these enol derivatives. For example, enol acetates were obtained by treatment of terminal acetylenes with mercuric acetate in acetic acid, followed by demercuration with $NaBH_4$ (eq. 14).



(14)

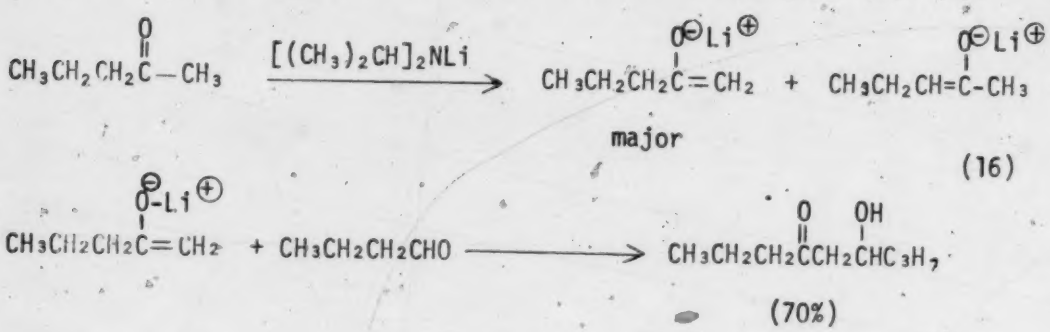
Z = OAc (85%)
= OMe (65%)
= N (20%)

Unfortunately, the regiospecific construction of terminal enol derivatives such as enol acetates, TMS enol ethers, etc. falls short of solving the problems associated with alkylation of a methyl alkyl ketone at the less substituted α position. For example, equation 15[33] illustrates that enolization of methyl alkyl ketone 20 with a hindered base, or cleavage of the corresponding mixture of trimethylsilyl enol ethers resulted in a mixture of enolates, and subsequent alkylation of the enolate mixtures produced substantial amounts of three byproducts (eq. 15).



House[33] explains that both the internal enolate and the enolate derived from the monoalkylated compound 22 react more rapidly than the starting terminal enolate. This slower rate of alkylation of terminal enolate 21b allows equilibration between the starting enolates and the alkylated products. This equilibration favors both the consumption of the desired monoalkylated product 22 and the formation of the byproducts. Based on these observations, House concludes that attempts to alkylate selectively at the methyl group of a ketone RCH_2COCH_3 by any method which involves generation of a terminal enolate $RCH_2C(O^-)=CH_2Li^{\oplus}$ will not be a good synthetic procedure and other indirect methods[32] should be used.

However, recent work by Stork and co-workers[41] demonstrates that terminal lithium enolates of methyl alkyl ketones can indeed be trapped with sufficiently reactive electrophiles such as aldehydes (eq. 16).

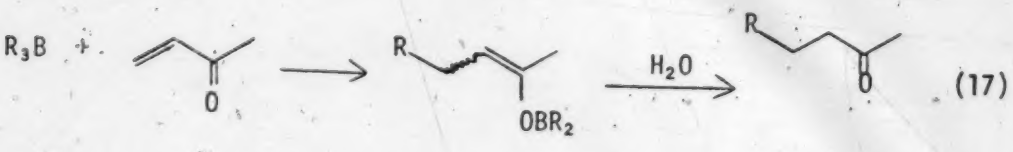


(16)

The reaction is carried out at low temperature (-78°) which apparently prevents equilibration of enolates. For less reactive electrophiles such as simple alkyl halides, however, the problem remains virtually unsolved.

The above discussion again demonstrates the need for a new synthetic approach, in which terminal enol derivative could be regiospecifically constructed and alkylated directly without first transforming it into a metal enolate.

We examined two independent routes for the regiospecific construction of terminal enol borinates. The first considered the reaction of ketone with trialkylboranes, by analogy with the reaction of α,β-unsaturated carbonyl compounds with an alkylborane[39] (eq. 17).

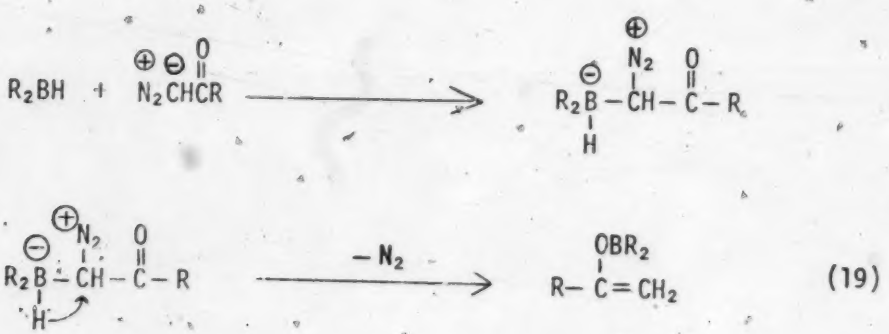


(17)

This proved unsuccessful although Mukaiyama and co-workers[42] have shown that thioboranes (like dialkylthioboronites) do undergo reaction with ketene (eq. 18) to yield the corresponding thioenolborinate.

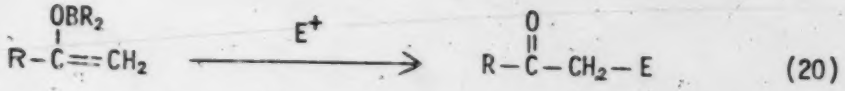
(18)

The second approach is essentially an extension of the trialkylborane-α-diazocarbonyl reaction (eq. 8). A study was made of the reaction of various dialkylboranes with α-diazoketones. The purpose of this project was to find a suitable dialkylborane which would a) be sufficient electrophilic to coordinate with diazoketones, and b) transfer "hydride" (rather than an alkyl group) (eq. 19) in an analogous manner to the R_3B-α-diazo reaction, thus allowing the regiospecific construction of terminal Mannich bases of methyl alkyl ketones.



(19)

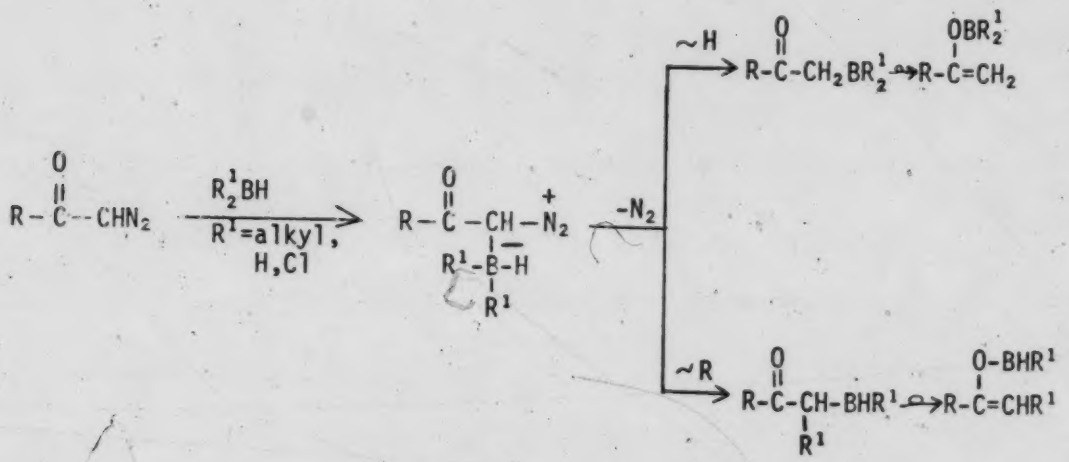
Indeed, after examining various dialkylboranes, we have found that dicyclohexylborane does undergo such a reaction with diazoketones, details of which are given in the next section. This development opens the way for the regiospecific synthesis of alkylated derivatives (β-aminoketones, etc.) in a manner which is synthetically equivalent to alkylation at the CH_3 group of a methyl alkyl ketone (eq. 20).



(20)

RESULTS AND DISCUSSION

By analogy with the reaction of trialkylboranes with α-diazoketones,[36] it was anticipated that the reaction of dialkylboranes with diazo substrates might also proceed by an initial coordination step. In this case, however, two subsequent possibilities exist: a) "hydride" transfer which would form a terminal enol borinate, and b) alkyl transfer which would result in an internal enol borinate (Scheme I).



Scheme I

To investigate this reaction as a potential route to terminal enol borinates, a series of borane derivatives were treated with several α-diazoketones.

Diborane was chosen first as it represents the simplest borane and is capable of transferring three hydrogens. When diazoacetophenone in THF was added to an equivalent of a borane-THF solution (-78°, 9 hr) an equivalent amount of gas (presumably N_2) was liberated. Mild

hydrolysis with methanol (-78°) released two additional equivalents of gas (presumably H_2) (eq. 21).

$$C_6H_5-\overset{O}{\overset{\|}{C}}-CHN_2 + BH_3 \longrightarrow N_2 + H_2 + C_6H_5-\overset{O}{\overset{\|}{C}}-CH_3 + C_6H_5-\overset{OH}{\overset{|}{C}}H-CH_3 + C_6H_5-CH_2CH_3 + C_6H_5-\overset{O}{\overset{\|}{C}}-H \qquad (21)$$

Glc analysis of the mixture indicated the formation of four products: acetophenone (28%), 1-phenylethanol (5%), ethylbenzene (15%) and a trace (ca. 3%) of benzaldehyde. The presence of ethylbenzene and 1-phenylethanol indicates that a reduction process takes place in addition to the anticipated reaction although there is no clear indication of how or at what stage of the reaction this competing process occurs. The most surprising and inexplicable result is the formation of a small amount (ca 3%) of benzaldehyde, which involves cleavage of a C-C bond.

The reaction was repeated using 0.33 equivalents of borane and essentially quantitative evolution (per B-H bond) of N_2 (98%) was detected. However, the yield of the expected product, acetophenone, was only 2%. This indicates that the intermediate enol borinate is either formed in an extremely minor amount or, if it is formed, it then undergoes further reaction to give intermediates which do not yield the ketone upon hydrolysis.

Table I

Reaction of $BH_3 \cdot THF$ with α-diazoketones

α-diazoketone	Molar Ratio BH_3 to ketone	Time of Reaction hr.	Temp C°	% N_2	$R-\overset{O}{\overset{\|}{C}}-CH_3$ [a]	$R-\underset{OH}{\underset{\|}{CH}}-CH_3$ [a]	R-CHO [a]	RCH_2CH_3 [a]
$C_6H_5\overset{O}{\overset{\|}{C}}CHN_2$	1:1	9	-78°	100	28 %	5 %	3 %	15 %
$C_6H_5\overset{O}{\overset{\|}{C}}CHN_2$	0.33:1	4	-65°	98	2 %	-	trace	18 %
$(CH_3)_2CH\overset{O}{\overset{\|}{C}}CHN_2$	0.33:1	5	-20°	67	15 %	-	-	13 %
$(CH_3)_2CH(CH_2)_2\overset{O}{\overset{\|}{C}}CHN_2$	0.33:1	2	- 5°	65	12 %	-	-	19 %

a. yield determined by glc analysis

Alkyl diazoketones apparently undergo similar reactions, although in this case only two products were detected, ketones and hydrocarbons (Table I, entries 3-4).

These observations suggested that it would be preferable to use "mixed" boranes, such as dialkyl(halo)boranes, or hindered alkylboranes, in an effort to suppress transformation of the enol borinate into other intermediates and prevent the reduction process which could arise from the presence of intermediate boranes bearing active hydrogens.

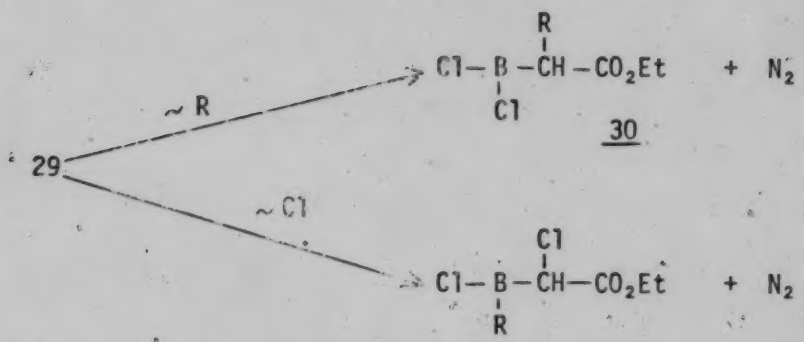
An analogous study has been reported by Hooz, Brown and co-workers[43] in the dichloroalkyl(aryl)borane-α-diazo reaction[36] (eq. 22). The

$$Ar(R)BCl_2 + N_2CHCO_2Et \longrightarrow Ar(R)CH_2CO_2Et \quad . \qquad (22)$$

advantage of this mixed organoborane over trialkylboranes is that the former permits the transfer of only one of three possible alkyl(aryl) groups, which maximizes the synthetic utility of this process. Thus, the reaction of ethyl diazoacetate with phenyldichloroborane in THF provided, after protonolysis, phenylacetate in 92% yield. However, repetition of this reaction with n-butyldichloroborane gave relatively poor results, 43% ethyl hexanoate and 30% ethyl chloroacetate. These results suggest a mechanism similar to that of the trialkylborane-α-diazo reaction, in which there is migration of chlorine as well as an alkyl group. After examining several other examples under various reaction conditions, these workers concluded that the order of migration aptitude is Ar>R>Cl. Such an order for aryl vs. alkyl had been previously observed in the rearrangement of α-haloboronates.[44]

$$RBCl_2 + N_2CHCO_2Et \rightleftharpoons Cl-\overset{\ominus}{B}(R)(Cl)-CH(N_2^{\oplus})-CO_2Et \quad (23)$$

29



(24)

30 31

In the light of these results we studied the reaction of dichloroborane[45,46,47] with diazoacetophenone. The dichloroborane was prepared by two different routes, in ether and THF, since solvent seems to be an important factor in the analogous reaction with $R(Ar)BCl_2$. In the first preparation, a solution of BCl_3 in ether was reduced by $NaBH_4$[46] (eq. 25). $BHCl_2$ in THF was obtained by

$$LiBH_4 + 3BCl_3 \xrightarrow{Et_2O} 4BHCl_2 \cdot Et_2O + LiCl \quad (25)$$

reaction of borane in THF with a standardized THF solution of HCl[45] (eq. 26).

$$BH_3 \cdot THF + 2HCl \cdot THF \xrightarrow{0^\circ} BHCl_2 \cdot THF + 2H_2 \qquad (26)$$

However, regardless of the mode of preparation or solvent, the reaction of $BHCl_2$ with diazoacetophenone (eq. 27) gave three products: acetophenone, chloroacetophenone, and 2-chloro-1-phenylethanol.

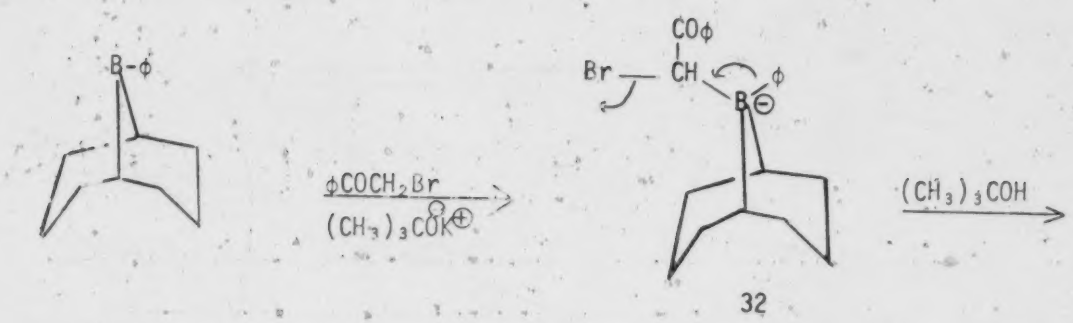
$$\phi\text{-}\overset{O}{\overset{\|}{C}}\text{-}CHN_2 + BHCl_2 \longrightarrow N_2 + \phi\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3 + \phi\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}Cl + \phi\text{-}\overset{OH}{\overset{|}{C}}H\text{-}CH_2\text{-}Cl \qquad (27)$$

(100%) (25%) (60%) (6%)

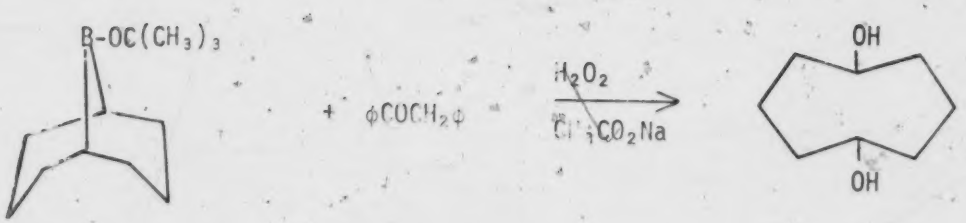
Acetophenone and the chlorinated products were presumably formed by hydrogen and chlorine migration respectively, in a fashion similar to the reaction of $RBCl_2$ derivative with diazo compounds.[43] The yield of the products indicates that the migration aptitude of chlorine is somewhat higher than that of hydrogen. Thus, one could extend the earlier observation to give an overall migratory aptitude of Ar > R > Cl > H.

Since the anticipated product, acetophenone, was obtained in relatively low yield, we then turned our attention to commonly used dialkylboranes such as: 9-borabicyclo[3·3·1]borane (9-BBN), bis (3-methyl-2-butyl)borane(disiamyl borane) and dicyclohexylborane as well as the monoalkylborane, 2,3-dimethyl-2-butylborane (thexylborane).

The migratory aptitude of alkyl vs. the cyclooctyl bond of B-alkyl-9-borabicyclo[3-3-1]nonane (B-R-9BBN) derivatives has been examined in several systems. In a series of communications[48] it had been demonstrated that B-R-9-BBN derivatives could be advantageously employed for alkylation of α-halo carbanions (eq. 28) as well as in carbonylation reactions.



32



(28)

On the other hand, B-R-9-BBN derivatives react with diazoacetone and ethyldiazoacetate,[49] respectively, to give a product derived exclusively from B-cyclooctyl bond migration. It was therefore of interest to study the behaviour of 9-BBN in our systems.

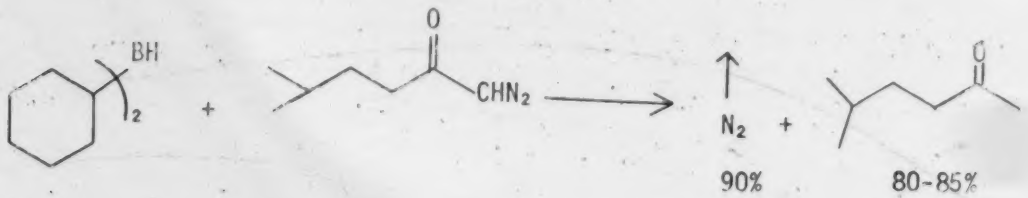
Addition of a THF solution of 1-diazo-5-methyl-2-hexanone to a THF solution of 9-BBN at 15° resulted in quantitative nitrogen evolution. However methanolysis of the crude mixture (hydrolysis and alcoholysis effectively cleave the B-O bond of enol borinates)[36], followed by glc analysis, did not indicate the presence of the anticipated ketone, 5-methyl-α-hexanone, which would have resulted from B-H bond migration.

In a variety of reaction of "mixed" thexylboranes, the thexyl group has been shown to migrate least readily.[50] However, experiments

with thexylborane indicated that this hindered monoalkylborane is unsuitable for use in our system. Extensive coloration occurred and only low yields of N_2 evolution was observed.

We then found that both dicyclohexylborane and disiamylborane undergo a reaction with alkyldiazoketones as anticipated. The use of dicyclohexylborane gave slightly higher yields in spite of the fact that the reaction with the latter is heterogenous.

After varying some reaction parameters, such as temperature, stoichiometry, and the duration of the reaction, we observed that the highest yields of ketones were obtained when the dialkylborane was used in slight excess (1.3:1) and the reaction was carried out in THF at 5° to 7°C for about 45 minutes (eq. 28).

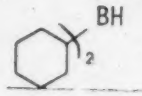
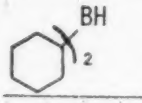
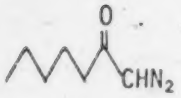
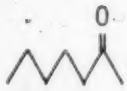
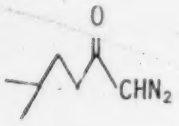
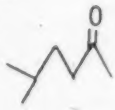
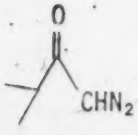
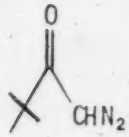
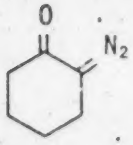
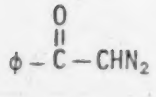
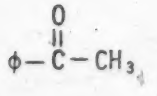


(28)

Using these conditions, the reaction was explored for several diazoketones and the results are summarized in table II. Clearly, steric factors play an important role in this system. The yield of ketone and hence precursor enol borinate progressively decreases with increasing steric bulk of the parent diazoketone.

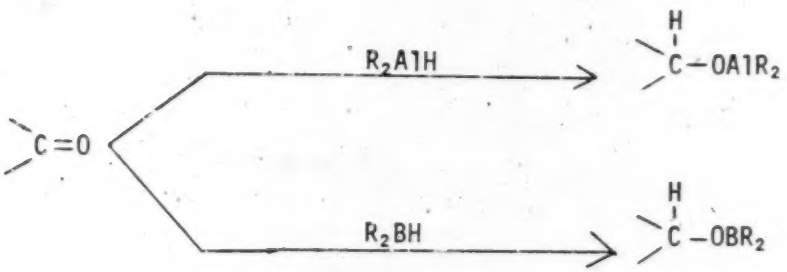
Table II

Reaction of diazoketone with dicyclohexylborane and disiamylborane

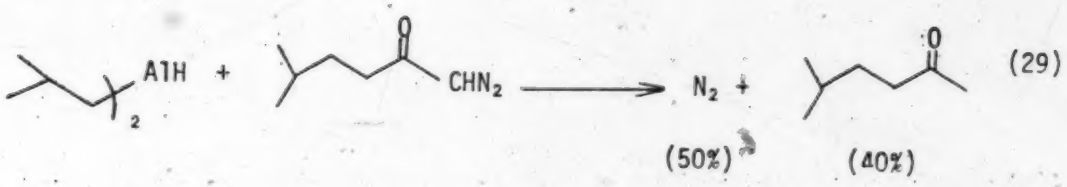
Diazo Compound	% N_2		Product	Glc Yield	
		Sia_2BH			Sia_2BH
	98	93		93%	89%
	90	81		85%	80%
	75	61		70%	59%
	25		*	*	
	20<	37	*	*	
	32	32		29%	29%

* Not detected by glc analysis

One attempt was also made to prepare an aluminum analog, e.g., $R_2Al\text{-}O\text{-}\underset{R}{\underset{|}{C}}=CH_2$. It was expected that such an intermediate could be formed using the appropriate dialkylaluminum hydride because in many instances organoaluminum compounds display chemistry similar to that of organoboranes. For example, both organoaluminum hydrides and dialkylboranes react with acetylenes[51,52] or ketones[51,53] in a similar fashion.



Thus it was interesting to compare the reactivity of an organoaluminum hydride with dicyclohexylborane in its reaction with an α-diazoketone. The reaction between diisobutylaluminum hydride and 1-diazo-5-methyl-2-hexanone was carried out in ether and THF. It was observed that the rate of the reaction is much slower than that of the organoborane and extensive coloration took place. In contrast to the organoborane, diisobutylaluminum hydride reacted faster in ether than in THF, although, in either solvent nitrogen evolution did not exceed 50% of the theoretical amount (eq. 29). It became clear at this point that dialkylboranes are more suitable hydride transfer reagents than diisobutylaluminum hydride and our



(29)

efforts were then concentrated on using dicyclohexylborane for the preparation and utilization of terminal enol borinates.

The observation that the intermediate enol borinate underwent rapid cleavage by water[36] (or MeOH) suggested the possibility of specific deuterium incorporation by employing deuterium oxide (or MeOD) as the hydrolytic medium. When the reaction of α-diazoketones with dicyclohexylborane was quenched with D_2O or MeOD, high yields of ketones with relatively high monodeuterium incorporation were obtained. The results are summarized in Table III. The NMR spectrum of the monodeuterated ketones exhibits a triplet at 7.8 τ with J = 2 Hz corresponding to the monodeuterated methyl group.

This preparation of 1-deuterio-2-alkylketones, complements the work of Gunn[54] who showed that α-deuterio esters and ketones 33 can be synthesized according to equation 30.

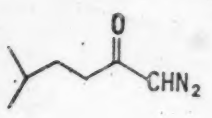
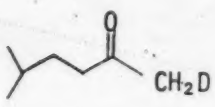
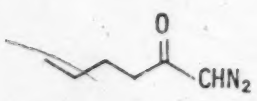
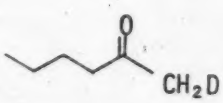
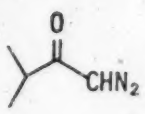
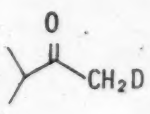
$$R_3B + N_2CHA \xrightarrow{D_2O} R-\underset{D}{CH}-A \qquad (30)$$

33

A = CO_2Et, $COCH_3$, $CO\phi$

Table III

Deuterium Incorporation of Methyl alkyl ketones

diazoketone	product[a]	Glc yield	% deuteration[b] d_o	d_1	d_2
		85%	7	82	11
		83%	17	79	4
		71%	20	77	3

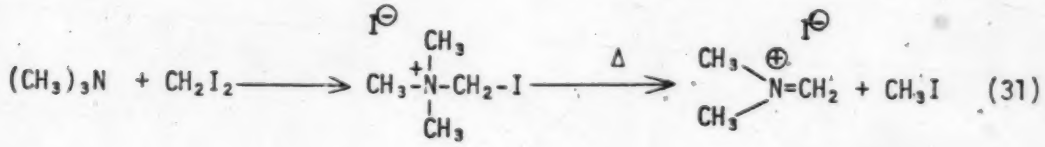
a. structure determined by NMR and mass spec.

b. determined by mass spec.

The high percentage of d_1 (as determined by NMR and mass spec) again indicates that the formation of the terminal enol borinate is a regiospecific process and that, under the reaction conditions employed, the intermediate does not undergo isomerization to the thermodynamically more stable enol. (The formation of small amounts of d_0 and d_2 is probably due to adventitious hydrolysis, and deuterium scrambling on glc column respectively.)

Having developed a route to terminal enol borinates, we turned our attention to the possible utilization of these intermediates for synthesizing the corresponding Mannich bases.

The Mannich reagent, dimethyl(methylene)ammonium iodide was prepared according to the procedure developed by Eschenmoser and co-workers[55] as illustrated in equation 31.



(31)

The reaction between a preformed enol borinate and the "Mannich reagent" proceeded under very mild conditions and gave good yields of β-aminoketones.

For example, sequential treatment of a THF solution of dicyclohexylborane with 1-diazo-5-methyl-2-hexanone in THF, followed (after nitrogen evolution ceased) by 1.15 equiv. of "Mannich reagent" (in DMSO)[+], afforded after a hydrolytic work-up a 92% yield (glc) of

---

+ The presence of DMSO cosolvent was crucial to the success of the reaction of internal enol borinates with the "Mannich reagent"[34] and was therefore routinely employed in the present study.

Table IV

Formation of Mannich Bases by Reaction of

Dimethyl(methylene)ammonium Iodide with Terminal Enol Borinates

Diazo ketone	Product	N_2, %	Yield[a], %	Picrate, mp°C
1-Diazo-2-heptanone	1-Dimethylamino-3-octanone	95	87	87 - 88
1-Diazo-5-methyl-2-hexanone	1-Dimethylamino-6-methyl-3-heptanone	100	92	97 - 98
Diazomethyl cyclohexyl ketone	1-Cyclohexyl-3-dimethylamino-1-propanone	80	80	119 - 120

a. Glc yields

1-dimethylamino-6-methyl-3-heptanone (Picrate m.p. 97-98°). Other examples are illustrated in Table IV.

As the results in Table II indicates, this preparation is not suitable for very hindered diazoketones, like diazomethyl-t-butyl ketone and for diazoacetophenone. However this drawback is not of major significance, since the conventional procedure for the synthesis of such Mannich bases can be employed as the corresponding parent ketones can be enolized in one direction only.

At the conclusion of this investigation, a recent report appeared on the regiospecific synthesis of terminal Mannich bases.[29] It was shown that relatively hindered methyl alkyl ketones (methyl cyclohexyl ketone and methyl isopropyl ketone) when reacted with di-isopropyl-(methylene)ammonium perchlorate in refluxing acetonitrile for 72 hrs. gave the corresponding terminal β-aminoketone in relatively high yields. However, since the reaction appears to be thermodynamically controlled (prolonged reaction time, hindered "Mannich reagent" etc.) it is limited to methyl-5-alkylketone systems, thus leaving the unhindered case untackled.

In conclusion, this investigation has shown that regiospecific construction of terminal enol borinate can be achieved by the reaction of dicyclohexylborane with diazoketones. Furthermore, this intermediate can be successfully employed in the regiospecific synthesis of terminal Mannich bases, compounds which are not easily obtainable otherwise.

EXPERIMENTAL

General Considerations

Infrared (ir) spectra were recorded using a Unicam SP1000 Infrared spectrophotometer. Nuclear magnetic resonance (nmr) spectra were run on a Varian A-60 or HR-100 spectrometer. Chemical shifts are reported as δ values relative to TMS=0. The following abbreviations are used in the text: s = singlet, d = doublet, t = triplet, and m = multiplet. Mass spectra were recorded on an AEI Model MS-9 spectrometer. Spectra are reported in the following fashion: m/e = peak mass (relative intensity).

Quantitative analytical gas liquid chromatography (glc) analyses were performed on Varian Aerograph Series 1200 and 1400 instruments versus a reference solution of the authentic compounds. Preparative glc work was performed on a Varian Aerograph A-90-P3 instrument.

Refractive indices were measured on a Bausch and Lomb Abbe-32 Refractometer.

The concentration of commercial borane-THF solutions (Alfa, 1M) were determined by hydrolysis with a water-ethyleneglycol mixture and measuring the H_2 evolution.[84,85]

In the synthesis of diazoketones[58,59,60], diazomethane was prepared by the method of Moore and Reed[57], using the modification of Hooz and Bridson.[58]

All operations involving boranes and aluminum compounds were carried out under an atmosphere of oxygen-free nitrogen.[56]

General procedure for the preparation of diazomethyl alkyl ketones - To a cooled (-5° to -10°) solution of diazomethane (ca 0.25 mol) in ether (700 ml) was added dropwise, with stirring, a solution of the acid chloride (0.07 mol) in ether (50 ml) over a 30 min period. The reaction mixture was then allowed to warm slowly to room temperature and was then stirred overnight. After removal of polymethylene by filtration, the resulting solution was dried (Na_2SO_4) and concentrated. The residue was then distilled under reduced pressure.

Preparation of diazomethyl isopropyl ketone - was prepared as described above from isobutyryl chloride (7.0 g, 0.060 mol) and diazomethane (ca 0.25 mol). Distillation (46-47°/4.0 mm) afforded 5.3 g (81%) of diazomethyl isopropyl ketone: n_D^{20} 1.4721 (lit[59] n_D^{20} 1.4727); ir (thin film) 2083 cm^{-1} (CH-N≡N), 1640 (C=O); nmr ($CDCl_3$): δ 5.34 (s, 1H) $-\overset{O}{\overset{\|}{C}}-CH-N_2$, 1.2 (d, J = 6.5 Hz, 6H) $(CH_3)_2C$, 2.5 (m; J = 6.5 Hz, 1H) $HC(CH_3)$.

Diazomethyl-t-butyl ketone was prepared as described above from t-butyrylchloride (4 g, 0.033 mol) and diazomethane (0.12 mol) in ether (250 ml). Distillation (50-51°/2.7 mm) afforded 3.1 g (78%) of diazomethyl-t-butylketone, n_D^{20} 1.4666; ir (thin film) 2083 cm^{-1} (CH-N≡N) 1640 (C=O); ($CDCl_3$) δ 5.34 (s, 1H) $-\overset{O}{\overset{\|}{C}}-CH-N_2$, 1.3 (s, 9H).

1-Diazo-5-methyl-2-hexanone was prepared according to the general procedure from 5-methyl-2-hexanoyl chloride (14.5 g, 0.11 mol) and diazomethane (0.35 mol) in ether (1300 ml). Distillation (50-51°/

0.5 mm, 64-65/1.7 mn) afforded 13.0 g (80%) of 1-diazo-5-methyl-2-hexanone n_D^{20} 1.4757; ir (thin film) 2083 cm^{-1} (CH-N≡N), 1640 (C=O).

Diazomethyl cyclohexyl ketone was made as described above from cyclohexane carboxylic acid chloride (1.12 g, 0.08 mol) and diazomethane (0.35 mol) in ether (1000 ml). Fractional distillation (75-76°/0.5 mm) afforded 9.0 g (80%) of diazomethyl cyclohexyl ketone: ir (thin film) 2083 cm^{-1} (CH-N≡N), 1640 (C=O).

1-Diazo-2-heptanone was prepared as described above from hexanoyl chloride (9.2 g, 0.067 mol) and diazomethane (0.35 mol) in ether (700 ml). Fractional distillation (bp 52-53/0.5 mn) afforded 7.5 g (80%) of 1-diazo-2-heptanone; n_D^{20} 1.4709; ir (thin film) 2083 cm^{-1} (CH-N≡N), 1640 (C=O).

Reaction of diborane with diazoacetophenone. A dry 50 ml flask equipped with a magnetic stirring bar, addition funnel and septum inlet was flushed with dry nitrogen and then connected to a gas-measuring device. The flask was cooled to -78° and charged with borane solution (4.25 ml, 1.18 M, 5 mmol) in THF (10 ml). To this solution was added, dropwise, (2 hr) a solution of diazoacetophenone (0.745 g, 5.1 mmol) in THF (20 ml). The reaction mixture was kept at this temperature for an additional 7 hr until the nitrogen evolution ceased. Then cold (-78°) methanol (20 ml) was added dropwise over a period of 30 min and the mixture was stirred (2 hr) until 2 equivalents of gas (presumably H_2) were collected. At this point the reaction

mixture was poured into sodium hydroxide solution (ca 2 M), the organic layer was separated and the aqueous phase was extracted with ether (3 x 30 ml). The combined organic phase was dried (Na_2SO_4) and the solution was concentrated at atmospheric pressure. The yield of acetophenone in the residue was determined as 28% by glc (20% DEGS, 150°). Three other minor components were identified by glc-mass spectral analysis and by glc peak-enhancement experiments with authentic samples as: benzaldehyde, ethylbenzene and 1-phenylethanol.

Reaction of dichloroborane with diazoacetophenone in THF. A solution of dichloroborane[45] in THF (12.6 ml, 0.396 M, 5 mmol) was placed in the apparatus described above. To this solution was added a solution of diazoacetophenone (0.74 g, 5.1 mmol) at -15° over a period of 2 hr. Nitrogen evolution was 100% (based on diazo compound). Methanol (10 ml, precooled to -20°) was then added and the mixture was stirred for an additional 30 min. At the end of this period the reaction mixture was poured into sodium hydroxide solution (ca 2 M), the organic layer was separated, and the aqueous phase was extracted with ether (3 x 20 ml). The combined organic phase was then washed with brine and dried (Na_2SO_4). After removal of solvent, the concentrate was analyzed by glc (20% DEGS, 180°). The three products were characterized both by peak-enhancement with authentic samples and by glc-mass spectral analysis as (in order of elution): acetophenone (25%) chloroacetophenone (60%) and 1-phenyl-2-chloroethanol (6%).

Reaction of dicyclohexylborane with diazoacetophenone. To a solution of BH_3 in THF (15 mmol) was slowly added cyclohexene (2.46 g, 30 mmol) in THF (15 ml) over a period of 20 min at 0°. A white precipitate formed, and the mixture was stirred at 0° for 1 hr. Then diazoacetophenone (2.2 g, 15 mmol) in THF (15 ml) was added, dropwise, (1 hr) at 5° to 10°. The solution gradually turned dark orange and N_2 evolution was only 32% of the theoretical amount. The reaction mixture was worked up as above and analysis of the residue by glc (20% DEGS, 150°) showed the presence of 28% of acetophenone.

Reaction of disiamylborane with diazoacetophenone. A solution of disiamylborane (10 mmol) was prepared by the hydroboration[86] of 3-methyl-2-butene (1.4 g, 20 mmol) in anhydrous THF (10 ml) at 0°C. The magnetically stirred mixture was kept at 0° for 1 hr and then allowed to warm to 5°. Then diazoacetophenone (1.43 g, 10 mmol) in THF (10 ml) was added dropwise (1 hr). The color of the solution gradually turned dark orange and nitrogen evolution was only 28% of the theoretical amount. The reaction was worked up as above, and glc analysis of the residue (20% DEGS, 150°) indicated a 24% yield of acetophenone.

Deuteration Experiments

1-Deuterio-2-hexanone - A dry 200 ml flask equipped with a magnetic stirring bar, addition funnel, and septum inlet was flushed with dry nitrogen and then connected to an azotometer. The flask was cooled to 0° and charged with a solution of borane in THF (24 mmol). To this solution cyclohexene (7.92 g, 48 mmol) in THF (20 ml) was added (70 min). A white precipitate formed and the mixture was stirred for 1 hr at 5°. Then 1-diazo-2-hexanone (2.52 g, 20 mmol) in THF (15 ml) was added, over 30 min. The reaction mixture was kept for an additional 1.5 hr at 5° to 7°, and nitrogen evolution was 93% of the theoretical amount (based on diazoacetophenone). Then D_2O (10 ml) was added and the mixture was kept at 5° to 7° for 30 min. The white solid which formed was filtered off and the organic phase was washed with water, then brine, dried (Na_2SO_4) and concentrated at atmospheric pressure. Analysis of the residue by glc (20% DEGS, 100°) showed the presence of 83% 2-hexanone; glc-mass spectra (20% carbowax 20M, 100°C) m/e: 102 (3, p+1), 101 (25, p), 100 (5, p-1), 86 (6), 85 (15), 75 (4), 72 (22), 71 (8), 60 (11), 59 (100), 58 (27). The percentage deuteration was determined as follows: The ratio of the peak heights (mm) when corrected for ^{13}C contribution (1.1% per carbon), of p-1:p:p+1 were considered as the proportions of undeuterated ketone: mono-: dideuterated ketone present in the mixture. A sample calculation is given as follows: Total contribution of ^{13}C for a C_6 is 6.6% (6 x 1.1). For the undeuterated ketone (d_0, m/e 100, 50 mm peak height) this requires no correction as there is no peak at m/e 99. For the monodeuterated compound (d, m/e 100, 241 mm peak height) this correction (6.6% of

50 mm) is 3.3 mm making the required peak height 238 mm. Similarly, for the dideuterated ketone/d_1, m/e 102, 28 mm peak height), this correction (6.6% of 238) is 15.7 mm, making the required peak height 12 mm. Thus, the percentage deuterium incorporation is, for d_o, $\frac{50}{(50+238+12)} \times 100 = 17\%$, for d_1 $\frac{238}{(50+238+12)} \times 100 = 79\%$ and for d_2 $\frac{12}{(50+238+12)} \times 100 = 4\%$. A sample was collected by preparative glc (20% DEGS, 100°C), nmr: δ 2.4 (t, J = 6 Hz, 2H) CH_2-C=O, 2.1 (t, J = 2Hz, 2H) $\overset{O}{\overset{\|}{C}}$-$CH_2D$, 0.8-1.8 (M, 9H) $CH_3CH_2CH_2$-.

1-deuterio-5-methyl-2-heptanone was prepared as described above from dicyclohexylborane (24 mmol) and 1-diazo-5-methyl-2-hexanone (2.81 g, 20 mmol). Glc analysis (20% DEGS, 100°) of the reaction mixture showed the presence of 83% of 5-methyl-2-heptanone. Glc mass spectral analysis m/e: 116 (1.2, p+1), 115 (8,p), 114 (1.1, p-1), 81 (5), 72 (11), 71 (5), 60 (17), 59 (100), 58 (13), 57 (35), 45 (90), 44 (70), 43 (4); present deuteration: d_o 5%, d_1 82%, d_2 11%; n_D^{17} 1.40020; NMR: δ 2.4 (t, J = 6 Hz, 6H) $-CH_2-\overset{O}{\overset{\|}{C}}$, 2.1 (t, J = 2 Hz, 2H) $\overset{O}{\overset{\|}{C}}$-$CH_2$-D, 1.4-1.6 (m, 3H), 1 (d, J = 7 Hz, 6H) $(CH_3)_2CH$.

1-deuterio-3-methyl-2-butanone was prepared from dicyclohexylborane (24 mmol) and 1-diazo-3-methyl-2-butanone (20 mmol) with the following modification of work-up. After nitrogen evolution ceased (82% based on diazoketone), MeOD (7 ml) was added and the reaction mixture was stirred at -20°C for 30 min. At the end of this period it was poured into a cool solution of $NaHCO_3$ (2M, 30 ml) and was extracted

with pentane (3 x 30 ml). The organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated at atmospheric pressure. Glc analysis (20% carbowax 20 m, 90°C) indicated a 71% yield of 3-methyl-2-butanone. Glc mass spectrum m/e: 88 (3, p+1), 87 (16, p), 86 (5, p-1); 71 (4), 56 (6), 55 (2), 44 (100), 43 (35), 41 (17); NMR: δ 2.3 - 2.5 (m, 1H) $-CH-\overset{O}{\overset{\|}{C}}$, 2.1 (t, J = 2 Hz, 2H), $\overset{O}{\overset{\|}{C}}-CH_2D$, 1.2 (d, J = 7 Hz, 6H).

Reaction of diisobutylaluminum hydride with 1-diazo-5-methyl-2-hexanone

To a solution of diisobutylaluminum hydride (Alfa, 1.42 g, 10 mmol) in ether (10 ml) was added dropwise, with stirring, 1-diazo-5-methyl-2-hexanone (1.41 g, 10 mmol) in ether (10 ml) over a period of 2.5 hr. Nitrogen evolution was only 50% of the theoretical amount and the reaction mixture gradually turned dark orange. The mixture was then carefully poured into ice-concentrated HCl (exothermic). After stirring for 15 min the two layers were separated. The aqueous phase was extracted with ether (3 x 30 ml) and the combined organic phase was washed with saturated bicarbonate solution, dried (Na_2SO_4), and evaporated. Analysis of the residue by glc (20% DEGS, 100°) showed a 40% yield of 5-methyl-2-hexanone.

Preparation of dimethyl(methylene)ammonium iodide[55] - A mixture of trimethylamine (10 g, 0.17 mol), diiodomethane (60 g, 0.21 mol), dioxane (10 ml), and anhydrous ethanol (75 ml) was kept in a closed vessel in the dark for 110 hr at room temperature. The crystals which formed were filtered off, washed with ethanol and then with

cold ether, and dried for 1 hr at 70°C/0.05 mm. (Iodomethyl)trimethylammonium iodide (49 g, 89%) was obtained as colorless crystals.

A suspension of the salt (40.0 g) in dry tetrahydrothiophene dioxide (120 ml) was placed in a dry four-necked flask fitted with a stirrer and thermometer and tube for passage of nitrogen, the exit tube leading to a cold trap (for MeI). The flask was flushed with N_2 and the reaction mixture was heated, while a slow stream of N_2 was passed in. The crystals dissolved rapidly at ca 130°C and the methyl iodide was conveyed by the N_2 stream into a cold trap, and the decomposition was completed in 15 min (ca 150°). On cooling, dimethyl(methylene)ammonium iodide crystallized directly from the yellow solution; it was filtered off under N_2, washed with CCl_4 (5 x 50 ml) and dried (50°/0.05 mm). This afforded 18.4 g (81%) of pale off-white crystals (dec. ca 240°C). Recrystallization from dry DMSO gave colorless crystals, dec. ca 240°C, ir (in nujol) 3115 cm^{-1} and 1682 cm^{-1} ν ($CH_2=N^-$); NMR (DMSO): two weakly broaded singlet at δ = 8.18 and 3.67 ppm in the intensity ratio 1:3.

Synthesis of 1-dimethylamino-6-methyl-3-heptanone. A heterogeneous mixture of dicyclohexylborane (10 mmol) was prepared by the hydroboration of cyclohexene (20 mmol, 1.64 g) in anhydrous tetrahydrofuran (10 ml). An azotometer was connected to the reaction flask and the mixture was cooled to 5°. The magnetically stirred mixture was maintained between +5 and +7° while a solution of 1-diazo-5-methyl-2-hexanone (1.0 g, 7.4 mmol) in THF (10 ml) was added dropwise over 30 minutes. Stirring was continued for an additional 30

minutes after which time nitrogen evolution was quantitative. Then a solution of dimethyl(methylene)ammonium iodide (1.85 g, 10 mmol) in anhydrous dimethylsulphoxide (10 ml) was added. The stirred reaction mixture was then allowed to warm to room temperature. After stirring at room temperature for 3 hr, the mixture was cooled to 0° and aqueous sodium hydroxide (15 ml of a 3N solution) was added. The mixture was stirred vigorously for 15-20 minutes, poured into ice-water (100 ml) and extracted with pentane (5 x 50 ml). After concentration of the extract, the residue was extracted with cold (-10°) 5N HCl (5 x 50ml) and the aqueous layer was made basic with a cold concentrated sodium hydroxide solution (10N). The basic mixture was then extracted with pentane (5 x 50 ml) and the yellowish brown residue remaining after concentration of the dried (Na_2SO_4) extract was distilled to afford 1-dimethylamino-6-methyl-3-heptanone (0.92 g, 73%) as a colorless liquid, b.p. 57-58/0.7 mn. n_D^{20} 1.4363, ir ($CHCl_3$) 2870 cm^{-1}, 2780 cm^{-1} (-N-CH_3, -N-CH_2-), 1710 cm^{-1} (C=O), NMR ($CDCl_3$): δ 0.88 (d, J = 5 Hz, 6H) -$CH(CH_3)_2$, 1.20-1.73 (broad resonance, 3H) C_5 and C_6 protons, 2.23 (S, 6H) $N(CH_3)_2$, 2.37 (m, 2H) C_4 protons, 2.59 (s, 4H) C_1 and C_2 protons. Mass spectrum m/e: 172 (0.2), 171 (1.1), 123 (3.0), 111 (120), 58 (100). Anal. calcd. for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18. Found: C, 70.38; H, 12.51; N, 8.23.

Picrate m.p. 97-98°C. Anal. Calcd. for $C_{16}H_{24}N_4O_8$: C, 48.00; H, 6.04; N, 13.99. Found: C, 48.10; H, 6.13; N, 14.01.

Synthesis of 1-cyclohexyl-3-(N,N-dimethylamino)-1-propanone. This was prepared as described above from 2-diazo-1-cyclohexyl-1-ethanone (1.22 g, 8 mmol). Distillation afforded the product (0.95 g, 68%) as a colorless liquid, bp 83-84/0.6 mm; n_D^{20} 1.4674; ir ($CHCl_3$): 2830 and 2795 cm^{-1} (-H-CH_3, -N-CH_2-), 1705 cm^{-1} (C=O); NMR ($CDCl_3$): 0.99-2.00 (broad resonance, 11H) cyclohexyl protons, 2.2 (s, 6H). NMe_2, 2.57 (s, 4H), protons at C_1 and C_3; mass spectrum m/e: 183 (1.6), 182 (1.3), 84 (80), 83 (5), 72 (5), 58 (100), 55 (14), 42 (16), 41 (15). Anal. Calcd. for $C_{11}H_{21}N_1O_1$: C, 72.08; H, 11.55; N, 7.43. Found: C, 72.34; H, 11.56; N, 7.64. Picrate: m.p. 119-120°C. Anal. Calcd. for $C_{17}H_{24}N_4O_8$: C, 49.51; H, 5.87; N, 13.59. Found: C, 49.65; H, 5.43; N, 13.80.

Synthesis of 1-dimethylamino-3-octanone. This was prepared as described above from 1-diazo-2-heptanone (1.0 g, 7.4 mmol). Microdistillation afforded the product (1.01 g, 80%) as a colorless liquid, b.p. 74.5-75°/1.5 mm; n_D^{22} 1.4388; ir ($CHCl_3$): 2820 and 2780 cm^{-1} (-H-CH_3, -H-CH_2-), 1710 (C=O); NMR ($CDCl_3$): δ 0.80-1.80 (methylene envelope, 6H) protons at C_5, C_6, C_7, 0.90 (t, 3H) C_8 protons, 2.23 (s, 6H) $H(CH_3)_2$, 2.37 (m, 2H) C_4 protons, 2.59 (s, 4H) C_1 and C_2 protons; mass spectrum m/e: 171.1617 (calcd. for $C_{10}H_{21}NO$: 171.1623), 172 (0.4), 171 (3.8), 84 (5.5), 72 (7.1), 60 (5.2), 59 (4.8), 58 (100), 57 (5.7), 55 (5.2). Anal. Calcd. for $C_{10}H_2NO$: C, 70.12; H, 12.36; N, 8.18. Found: C, 70.38; H, 12.51; N, 8.23. Picrate: m.p. 87-88°. Anal. Calcd. for $C_{16}H_{24}N_4O_8$: C, 48.00; H, 6.04; N, 13.99. Found: C, 48.22; H, 6.12; N, 13.71.

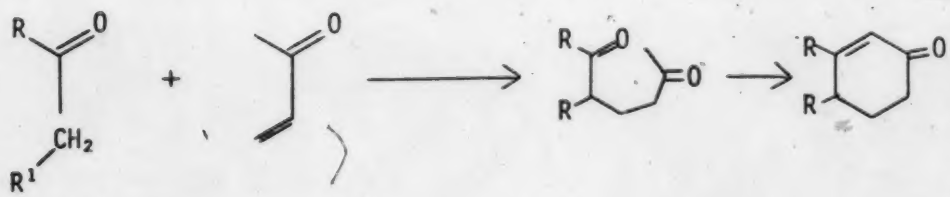
CHAPTER II

THE USE OF γ-ALKYL(PHENYL)THIOCROTYL CHLORIDES AS "OXO-BUTYL" EQUIVALENTS IN ANNELATION REACTIONS

INTRODUCTION

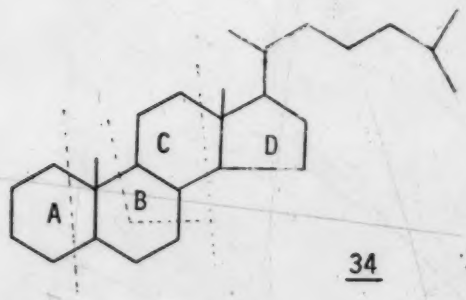
The Robinson annelation reaction[8,9,10] is a particularly powerful synthetic tool for the construction of six membered ring systems. In this reaction, ketones are condensed in a two stage base catalyzed process with an α,β-enone, as illustrated for methyl vinyl ketone (MVK) according to scheme II.

Scheme II



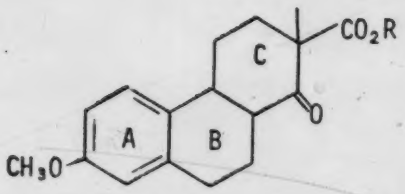
Among all the known methods for the synthesis of fused hydroaromatic ring systems, the Robinson annelation reaction holds a position of particular importance, since virtually all the successful total syntheses of natural non-aromatic steroids (and many other polycyclic natural products) have relied on this reaction at some stage.

As early as 1936, Robinson and his collaborators[8] pointed out that the reaction sequence could theoretically be used to build up the rings A, B, and C of the steroid skeleton, each stage of the cyclohexanone constructed being followed by reduction. Robinson proposed that, starting from a methylcyclopentanone derivative (ring D), the addition of ring C would require methyl vinyl ketone, then ring B is added by means of ethyl vinyl ketone, and ring A with methyl vinyl ketone again. This proposal is represented schematically by dissection of the steroid skeleton into four major units as illustrated by structure 34.

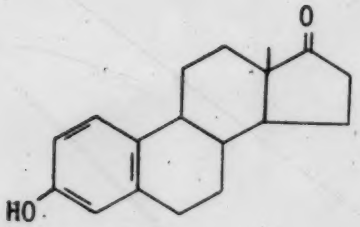


34

Applying of this sequence of reactions in the opposite direction (i.e. starting from the A-B ring system), Robinson and his collaborators[61] had produced a key tricyclic intermediate 35 and the completion of the fourth ring D to produce the estrone structure 36 appeared imminent. But there were still problems to overcome, and not until a dozen years later, and after many contributions from various laboratories were made, that the final goal was achieved.



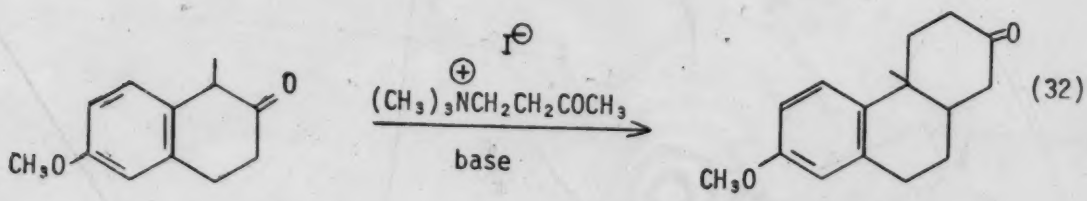
35



36

These extraordinary difficulties detering the total synthesis of this molecule with four asymmetric centers were mainly stereochemical in nature.

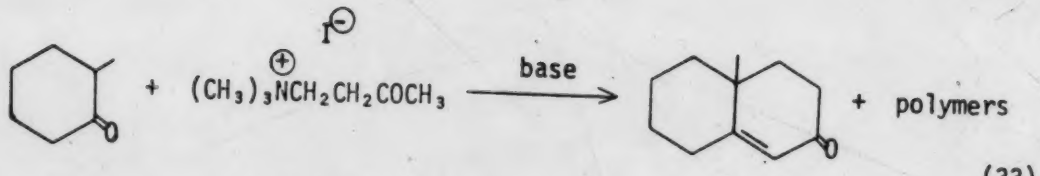
Although the Robinson annelation provides a direct route to fused ring ketones (eq. 32), the application of this method to cyclohexanones such as 2-methylcyclohexanone[62] has proven to be generally



(32)

(85%)

unsatisfactory. For example, the Robinson synthesis of 10-methyl-1(9)-octalone-2 (39)[8] and variations thereof[62] proceeds in low yield, requires a two or threefold excess of 2-methylcyclohexanone[8] and affords a product of questionable purity[63] (eq. 33).



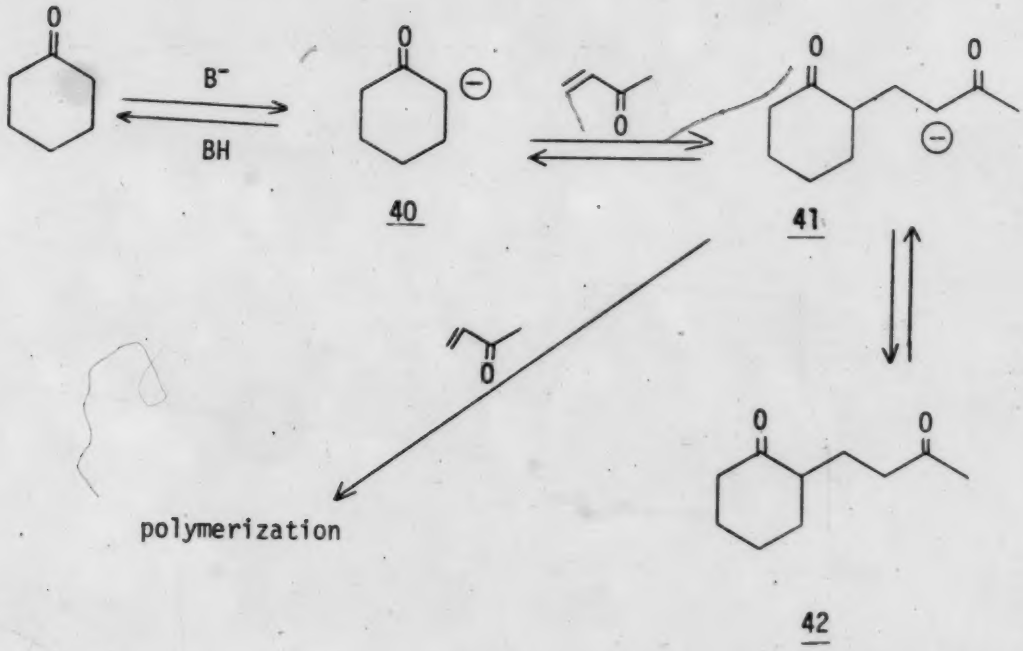
37 38 39 (38%) (33)

The difference between these two cases (eq. 32 and 33) lies in the nature of the saturated ketone. In the first example (eq. 32) the hydrogen lost during enolization of the ketone is more acidic than that of 2-methylcyclohexanone. Therefore milder reaction conditions are required for the enolization step, resulting in less complications and hence a higher yield of adduct.

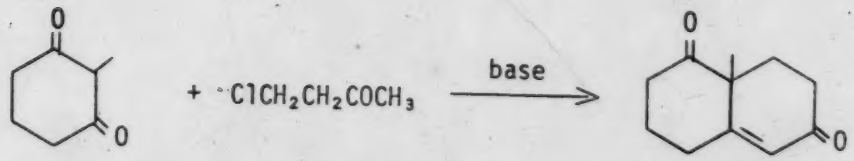
Basically, there are two main problems associated with using relatively weakly acidic cyclohexanones (which are not α-substituted with electron withdrawing groups). Firstly, the vigorous reaction conditions required for enolization may also affect the polymerization of the Michael acceptor. Secondly, the similarity in base strengths and reactivities of the enolate ion derived from both the starting material and adduct may lead to several competing reactions and subsequent polymerization (scheme III).

One method to diminish the effect of the first problem (namely, polymerization of the α,β-unsaturated ketone) is to employ a precursor that will slowly generate the Michael acceptor under the basic reaction conditions. In this manner only low concentrations of the enone are present at any given time, and polymerization is suppressed. Precursors which have been found effective are the

Scheme III



methiodide 38 and the α-chloroketone[64,69] 43. This modification appears quite satisfactory for relatively acidic ketones (eq. 32, 34) but not for simple cyclohexanones where other side reactions prevail.

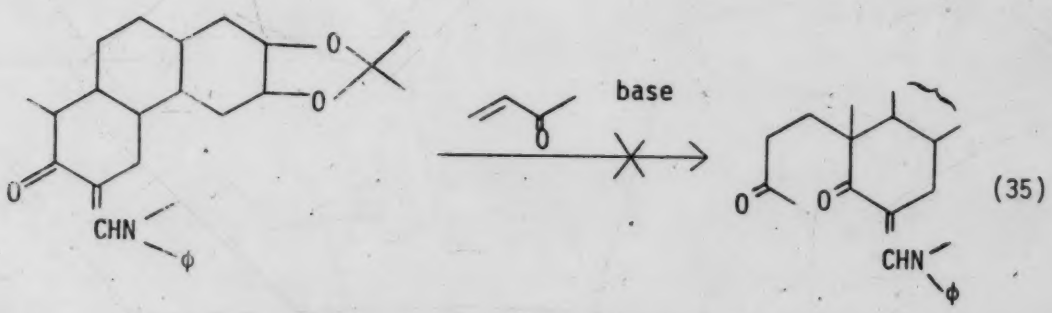


(34)

43

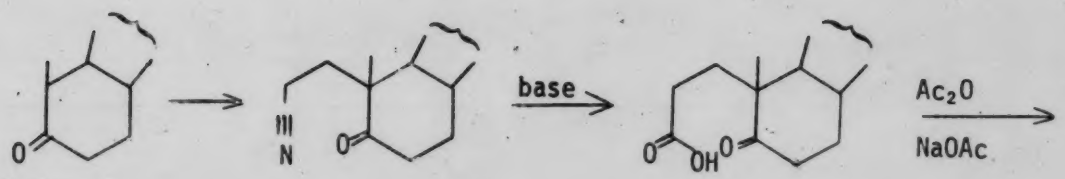
85%

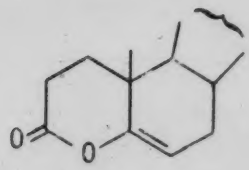
For systems which are even less acidic than simple cyclohexanones (eq. 35) the direct reaction (using MVK) or the modified one is virtually futile. Woodward and co-workers[65] experienced this difficulty as they endeavoured construction of ring A of cortisone using intermediate 44. Woodward explains that the hydrogen at C-10 is only weakly activated due to interaction of the amine group with the carbonyl, viz, O=C–C=C–N .



44 45 (35)

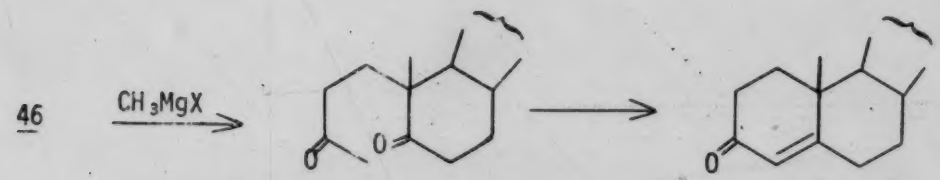
Consequently, strongly basic conditions were required for generating the corresponding anion, and this resulted in polymerization of methyl vinyl ketone. This difficulty was overcome by use of the Fujimoto reaction,[66,67,68] wherein the 4-carbon chain is introduced sequentially. This procedure involves initial α-alkylation of the ketone by an acrylic acid equivalent (usually acrylonitrile) followed by enol lactonization, then opening the enol δ-lactone with a methyl Grignard reagent and finally cyclization of the 1,5-diketone (eq. 36).





(36)

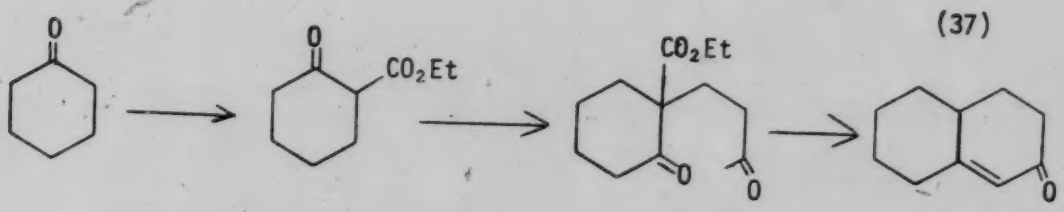
46



In the past two decades many modifications of the original Robinson annelation reaction have been introduced. These modifications can be classified into two major categories. One category attempts the improvement of the first stage of the Robinson annelation, namely the Michael reaction. The other category explores the use of "masked" keto alkyl equivalents in annelation reactions.

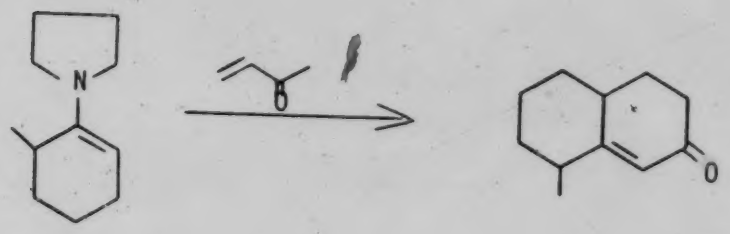
The efficiency of the Michael addition can be improved either by increasing the reactivity of the parent ketone or by employing certain α-substituents in the Michael acceptor which can stabilize the resulting enolate, thus preventing polymerization of the Michael adduct. One simple method of increasing the yield of annelation product is to incorporate an α-activating group in the Michael donor. The acidity

of the α-hydrogen is thereby enhanced, and the addition takes place more efficiently. For example, in the case of cyclohexanone, the desired octalone was obtained in 50% overall yield by first converting the ketone to 2-carbothoxycyclohexanone[30,70] (eq. 37), whereas without this modification,[30] the octalone was obtained in only 10% yield.



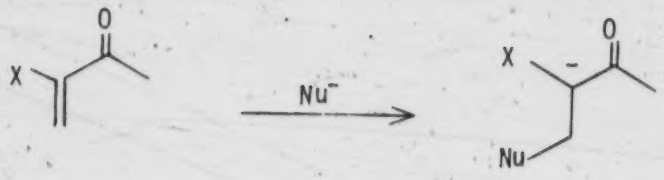
(37)

Similarly, the use of a pyrrolidine enamine avoids the problems of polyalkylation,[30] although, like the previous example, it is not applicable to the annelation of alkylcyclohexanones at the α-substituted site (eq. 38).



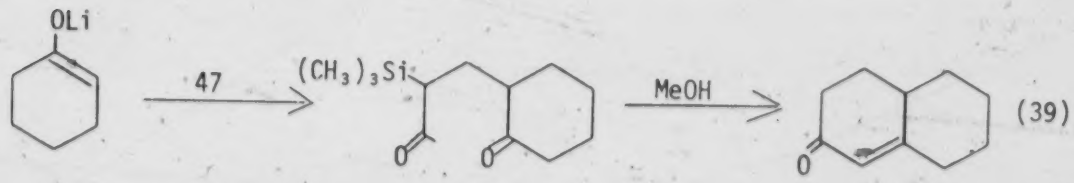
(38)

Recently, Stork and co-workers[71] examined the possibility of employing α-substituted vinyl ketones of the type 47 in which the substituent X would be capable of stabilizing the resulting enolate 48, thus preventing polymerization of the Michael adduct.



47 48

α-Silylated vinyl ketone 47 (X = $(CH_3)_3Si$) was chosen as the Michael acceptor for two reasons: a) an expectation that silicon, with its vacant 3d dorbitals, can stabilize an adjacent negative charge;[72] and b) that the stabilizing Si-group would be easily removed during completion of the annelation process. Thus the lithium enolate of cyclohexanone, when reacted with 47 at -78°C, gave the adduct 49. Treatment of 49 with 5% sodium methoxide-methanol resulted in cleavage of the "stabilizing" group and cyclization to the desired octalone in 80% overall yield (eq. 39).

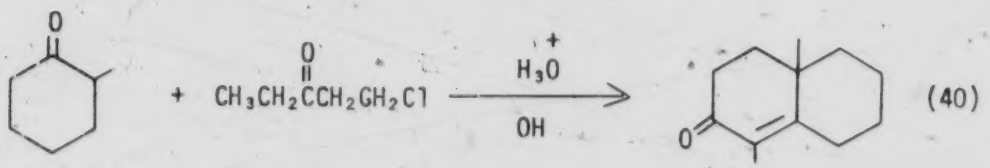


(39)

49

In subsequent publications Stork and co-workers[73] and Boeckman[74,75] demonstrated that methyl-α-trialkylsilylvinyl ketones can be condensed with regiospecifically generated lithium and copper enolates. This development has important implications for the total synthesis of steroids as well as for certain octalones which are not easily obtainable otherwise.

Another interesting modification of the Robinson annelation reaction involves the use of acid, rather than base, as a catalyst for both the Michael and aldol stages of the sequence. Heathcock and Ellis[76] showed that the annelation can be carried out directly with methyl vinyl ketone in the presence of sulfuric acid. Similarly, Zoretic and co-workers[77] reported the use of β-chloroketones and β-hydroxyketols as the "Michael acceptors" (eq. 40).



(40)

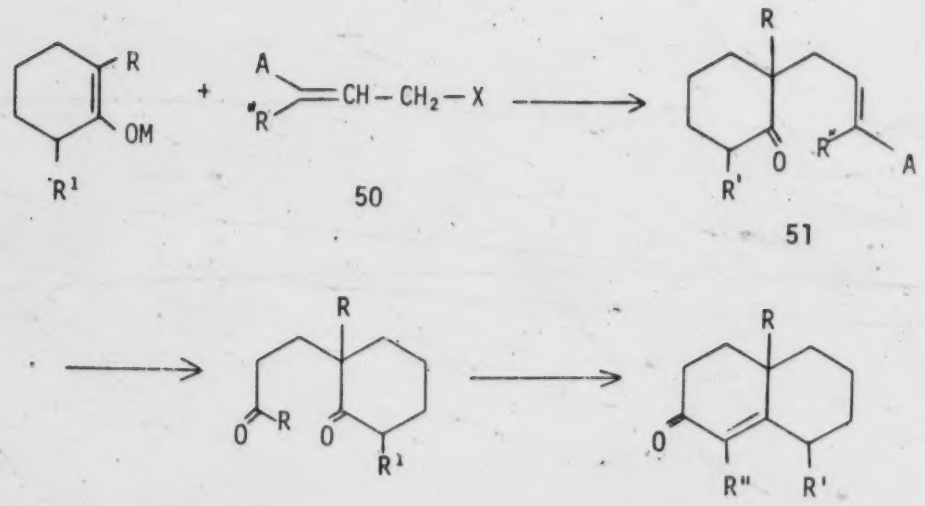
32-52%

However, the generality of this approach cannot as yet be assessed as only few examples have been reported to date.

The use of "oxo-butyl" equivalents[17,18,79,80,81] in the Robinson annelation has become increasingly important in recent years. Although this strategy appears in a variety of forms, these annelations are characterized by two common stages. The first involves alkylation of an enolate with a "masked ketoalkyl" reagent[47] and the second involves "unmasking" of the keto group followed by intramolecular aldolization of the 1,5-dicarbonyl system (Scheme IV).

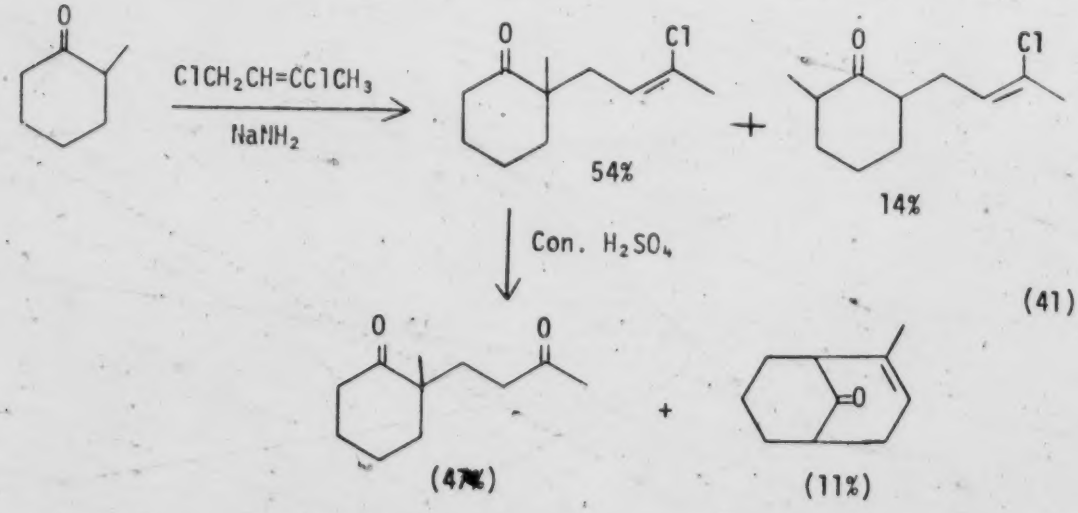
The first example of such an approach is the Wichterle reaction[78,17,19,20] which involves alkylating an enolate with 1,3-dichloro-2-butene. For example, Marshall and co-workers[17] used

Scheme IV



R, R', R" = H, alkyl.

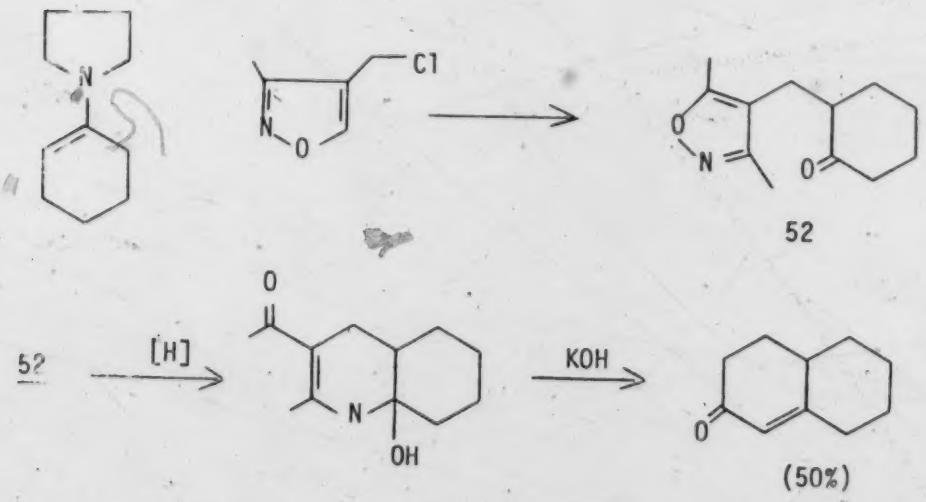
this scheme to introduce the required four carbon chain by alkylating the enolate of 2-methylcyclohexanone. The resulting vinyl chloride was then hydrolyzed with concentrated sulfuric acid to form a 1,5-diketone which was subsequently cyclized to the corresponding octalone (eq. 41).



(41)

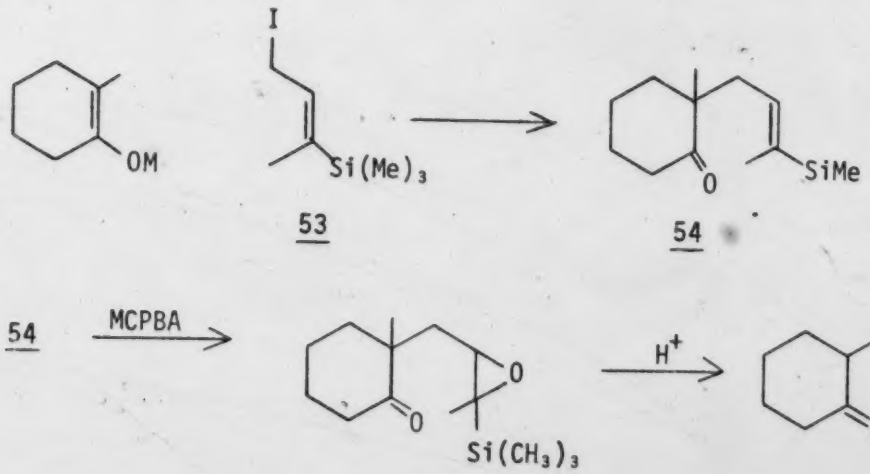
Unfortunately, the conditions required for the hydrolysis of the 2-(γ-chlorocrotyl)cyclohexanone often result in the formation of bicyclo[3.3.1]nonane derivatives as by-products. In fact, 2,6-dimethylcyclohexanone gave only the bridged bicyclo compound when subjected to the above procedure. Moreover, the initial alkylation step in this system is not a regiospecific process because of enolate equilibration, etc, as discussed earlier.

Soon afterwards Stork and co-workers[18] developed a rather lengthy procedure which overcomes the shortcomings mentioned in Marshall's scheme. In this approach, the active methylene compound is alkylated with chloromethylisoxazole derivatives and the product is reduced and annelated as indicated in equation 42.



During and since completion of the work done in this thesis, two new methods have been described.[80,81] In the first, Stork and Jung[80] investigated halomethyl vinylsilane 53 as an alkylating agent in annelation reactions. This strategy was based on previous

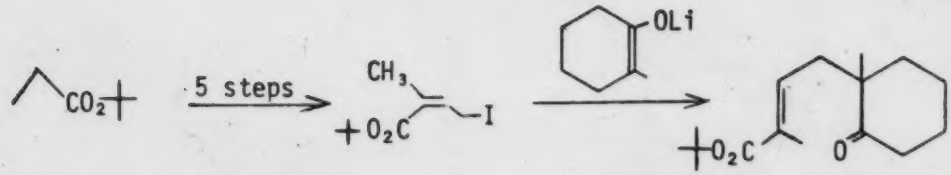
observations that vinylsilanes are readily transformed to carbonyls via epoxidation to an epoxysilane followed by acid treatment (eq. 43).



The main drawback of this approach lies in the fact that it involves a multi-step preparation of the alkylating agent; nevertheless this scheme is successful in obtaining high yields of various octalones.

Stotter and Hill[81] have also introduced an interesting variation of an "oxo-butyl" equivalent (eq. 44) by employing γ-iodotiglate 55 as the alkylating agent. Although this approach provided the enones in relatively high yield, it involves lengthy procedures both for the preparation of the required halide and in the "unmasking" process.

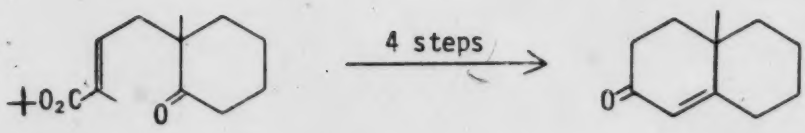
The annelation of ketones via "oxo-butyl equivalents" as alkylating agents has attracted our attention for some time. We have sought to develop an alternative to the Michael-Robinson process which would: a) provide a ketoalkyl equivalent from readily available



(44)

55

(90%)



(80%)

starting materials; b) be reasonably reactive toward regiospecifically generated enolates; and c) allow for readily "unmasking" into the required carbonyl function.

With these considerations in mind, γ-alkyl(phenyl)thiocrotyl chloride systems appeared to be attractive candidates for this reaction. As allylic halides they offered promise of high reactivity in alkylation of structurally specific enolates (thereby reducing the normal complications mentioned previously). Furthermore, the several procedures for the hydrolysis of vinyl sulfides described in the literature[82,83,88] made this choice especially attractive as this method would not be limited to one particular route for unmasking the desired ketone.

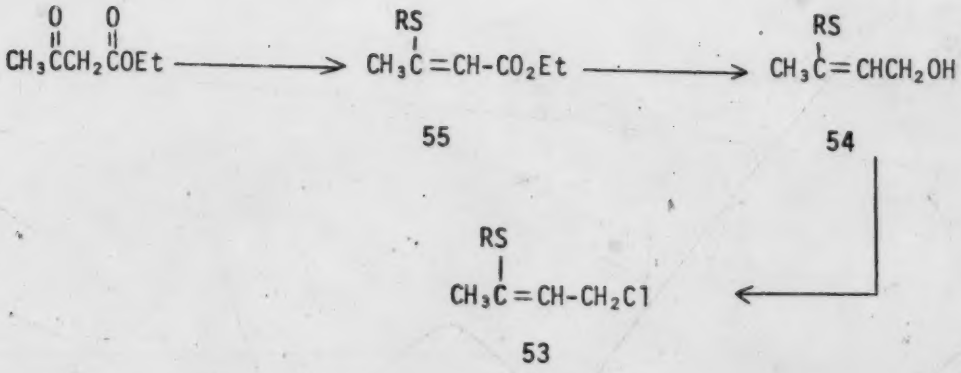
We have therefore prepared and studied the alkylation reaction of alkyl(phenyl)crotyl halides with several regiospecifically generated enolates. Subsequently, we investigated different routes for releasing the "masked" carbonyl and the cyclization to the desired octalones.

RESULTS AND DISCUSSION

Preparation of γ-phenyl(n-butyl)thiocrotyl chlorides

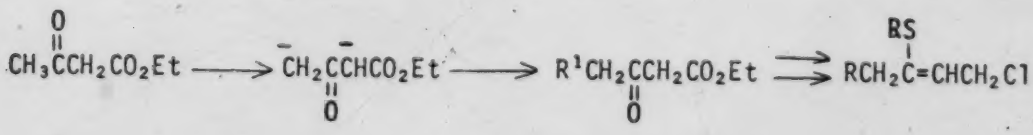
The route selected for the synthesis of the 3-ketobutyl equivalent is illustrated in scheme V. This scheme appeared attractive since it

Scheme V

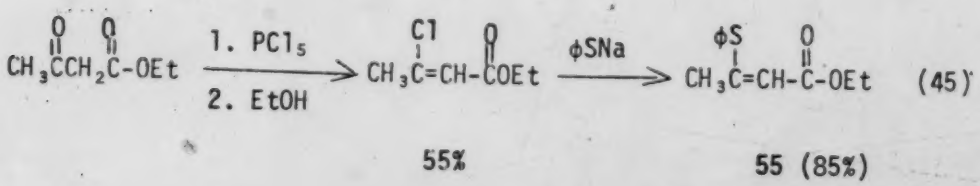


R = n-C_4H_9, C_6H_5

utilizes a readily available starting material and involves only three steps. Also, if successful, it offered the possibility of simple extension to the synthesis of other 3-ketoalkyl equivalents via dianion alkylation,[91] viz.,



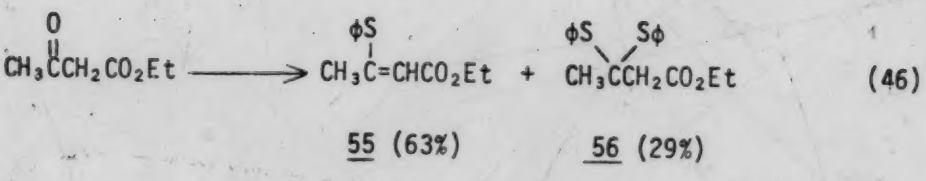
Initially, the vinyl sulfide 55 was prepared according to the procedure of Vernon and co-workers,[90] who reported that ethyl 3-chlorocrotonate undergoes relatively rapid nucleophilic displacement of halogen with the sodium salt of alkyl and phenylthiols. However, the preparation of ethyl β-chlorocrotonate was rather inefficient. It was originally obtained by reacting ethyl acetoacetate with two equivalents of phosphorous pentachloride, followed by hydrolysis to give β-chlorocrotonic acid. This was esterified (EtOH, H^+) in a separate step, resulting in a 30% overall yield. We modified this procedure by quenching the reaction mixture of ethyl acetoacetate and phosphorous pentachloride with excess cold ethanol. This gave directly ester 55 in about 55% yield (eq. 45).



55%

55 (85%) (45)

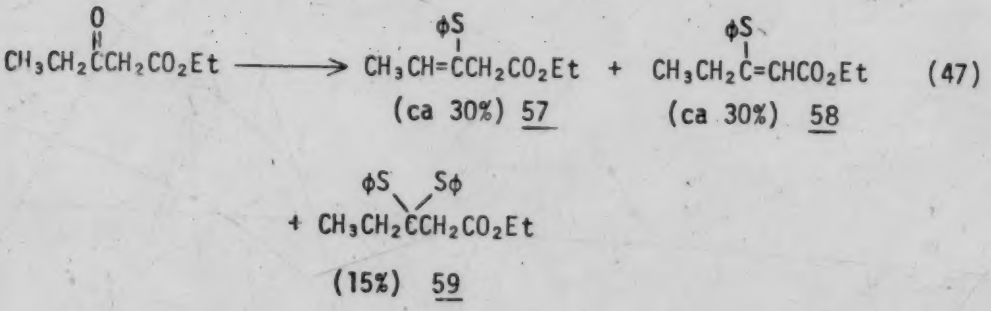
Subsequently, a direct and simpler preparation of 55 was investigated. Ethyl acetoacetate, one equivalent of benzenthiol, and a catalytic amount of p-toluenesulfonic acid was refluxed in benzene (10 hr) with azeotropic removal of water. This afforded the desired ethyl β-phenylthiocrotonate in 63% as well as diphenyl thioacetal, 56, in 29% yield, easily separable by distillation (eq. 46). Vinyl sulfide 55 was shown (by ir and nmr spectra, see Experimental) to be a mixture (50:50) of the E and Z isomers (Z isomer, b.p. 127-129/1.5 mm, E isomer, b.p. 134-136/1.5 mm).



(46)

55 (63%) 56 (29%)

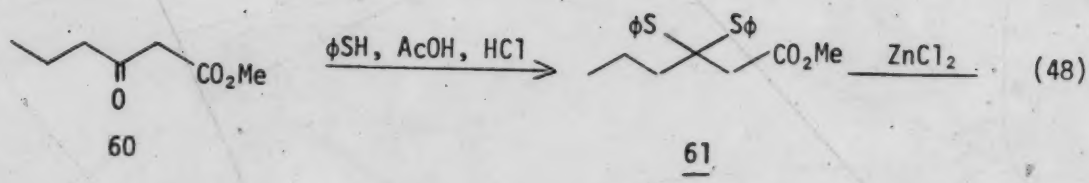
However, when this reaction was repeated with the next higher homolog, (from methylation of acetoacetic ester dianion[91]) three products were formed (eq 47). On the basis of spectral data (see Experimental) these were shown to be the β,γ- and α,β-unsaturated esters 57 and 58 respectively, as well as diphenylacetal 59. Since



(47)

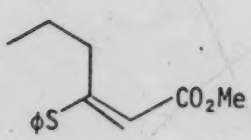
this resulted in a mixture of two positional isomers, this approach was discontinued. Other results of this study are given in Table IV.

After completion of this work, Mukaiyama and co-workers[92] recently observed that diphenylthioacetal 61 (prepared from β-keto-ester 60 and benzenethiol), when heated to 110°C in the presence of a catalytic amount of $ZnCl_2$, eliminated benzenethiol to form esters 62 and 63 (eq. 48). Also, compound 63 could be isomerized to 62 (in unstated yield) on treatment with potassium tert-butoxide in tert-

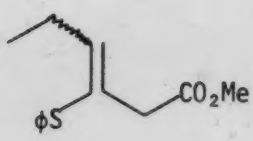


(48)

60 61



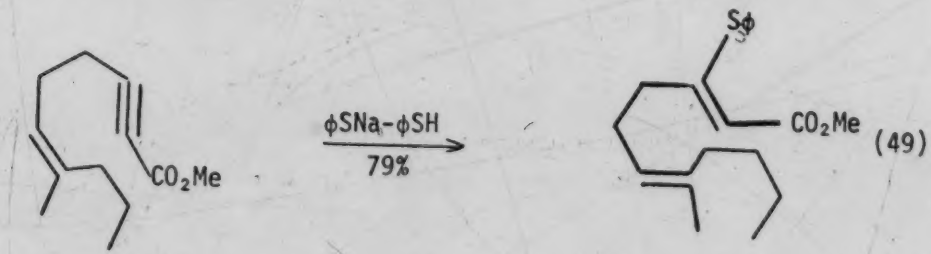
62 (31%)



63 (20%)

butyl alcohol. Should Mukaiyama's isomerization prove to be an efficient procedure, the dianion route would then become a practical alternative route to 3-ketoalkyl equivalents.

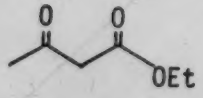
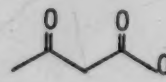
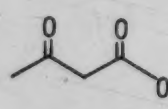
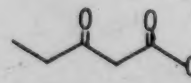
Another approach to the synthesis of phenylthio-α,β-ethylenic ester derivatives is the base catalyzed addition of thiolate anion to α,β-acetylenic esters.[92,93,94,95] This has been used as one step in a recent synthesis of a C_{18}-juvenile hormone analogue (eq. 49).



(49)

Table V

Preparation of β-alkyl(phenyl)thio-α,β-ethylenic esters

Substrate	Reagent	Total yield*	α,β-isomer	β,γ-isomer	thioacetal ester
	ϕSH/DTSA	82%	63%	-	19%
	ϕSH/BF_3	50%	37%	-	13%
	n-BuSH/PTSA	74%	59%	-	17%
	ϕSH/PTSA	75%	30%	30%	15%
$CH_3C(Cl)=CHCO_2Et$	ϕS^-Na^+	85%	85%	-	-
$CH_3C(Cl)=CHCO_2Et$	n-BuS^-Na^+	85%	85%	-	-
$\phi CH_2CH_2C\equiv C-CO_2Et$	ϕS^-Na^+	88%	40%	48%	-

* isolated yield

This route became potentially attractive especially after the recent development of a new propargylation reaction in our laboratory.[96] Calzada has demonstrated that dilithiation of allene produces a species "$C_3H_2Li_2$" which serves as an anionic propargylating reagent, "$LiCH_2C{\equiv}CLi$". This can be utilized for a "one pot synthesis" of either propargyl alcohols or esters. For convenience, the model selected for conjugate addition of benzenethiol was the product of benzylation ($C_6H_5CH_2Cl$) and subsequent <u>in situ</u> carboethoxylation of the "propargyl dianion" (eq. 50).

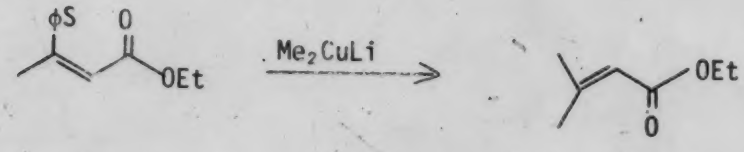
$$CH_2{=}C{=}CH_2 \xrightarrow{n\text{-}BuLi} LiCH_2C{\equiv}CLi \xrightarrow{C_6H_5CH_2Cl} \phi CH_2CH_2C{\equiv}CLi \xrightarrow{ClCO_2Et} \phi CH_2CH_2C{\equiv}C\text{-}CO_2Et \quad (50)$$

(80%)

In our hands, however, attempted base catalyzed addition of benzenethiol to ethyl 5-phenyl-2-pentynoate resulted in a mixture of the two positional isomers (as evidenced by nmr and ir spectroscopy, see Experimental). Again, should the isomerization to the α,β-ethylenic ester prove to be practical, this alternative route is potentially useful for the synthesis of β-alkyl(phenyl)thio-α,β-ethylenic ester derivatives. Since these compounds are homologs of ethyl β-phenyl(alkyl)thiocrotonate, they can be employed in the synthesis of 1-alkyl-$\Delta^{1,9}$-2-octalones, which, of course, extends the scope of the octalone synthesis.

Next, several methods for the reduction of β-phenyl(<u>n</u>-butyl)-thiocrotonates to the corresponding alcohols were examined.

Lithium aluminum hydride (LAH) proved to be unsuitable since the reaction between ethyl β-phenylthiocrotonate (THF, 20°) and LAH afforded only poor yields (ca 10%) of the desired alcohol, 3-phenylthio-2-butene-1-ol, and benzenethiol was formed in significant amounts. The benzenethiol presumably arises by an addition-elimination reaction. Analogously, Posner and Brunelle[98] have shown that ethyl β-phenylthiocrotonate undergoes a similar reaction with "nucleophiles" such as dialkylcopper lithium reagents to afford β-alkyl crotonates (eq. 51).



(80%) (51)

Subsequently, diisobutylaluminum hydride (DIBAH)[99,100,101] and aluminum hydride[102-105] (non-nucleophilic reducing agents) were employed. The reduction with DIBAH was carried out in benzene, ether, and THF as solvents. The yield of alcohol progressively increased with increasing polarity of the solvents (Table VI). Nevertheless, the highest yield recorded was only 70%.

Aluminum hydride in ether prepared by Schlesinger's method[105] (eq. 52) produced an 80% yield of the desired alcohol. Based on the DIBAH study, it was anticipated that the yield might be further improved in THF. Aluminum hydride in THF was then prepared by

$$3LiAlH_4 + AlCl_3 \xrightarrow{\text{ether}} 3LiCl + 4AlH_3 \qquad (52)$$

modifying the Schlesinger procedure.[105] Instead of directly adding aluminum chloride to a suspension of LAH in THF (an extremely exothermic reaction) the reagent was prepared by adding a preformed aluminum chloride-THF solution to a suspension of LAH at 0°C. The resulting mixture proved highly effective for the reduction (eq. 53) and yields of 90 - 97% of alcohols (as E- and Z-mixtures) were obtained.

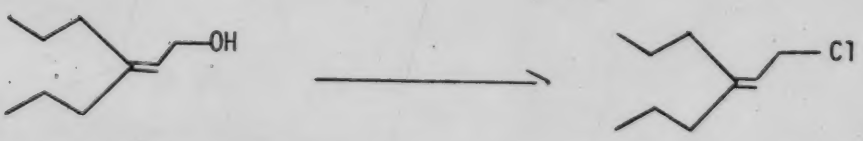
$$CH_3-\overset{\overset{RS}{|}}{C}=CH-CO_2Et \xrightarrow{AlH_3.THF} CH_3-\overset{\overset{RS}{|}}{C}=CH-CH_2-OH \qquad (53)$$

R = ϕ 90 - 93%

R = n-Bu 95 - 97%

The conversion of the allylic alcohols to the corresponding halides was anticipated to be a difficult step because such conversions are often accompanied by allylic transposition. Therefore, several recent mild procedures were investigated which have been shown to overcome this difficulty.

Meyer's method[106] involves treatment of an allylic alcohol in s-collidine with lithium chloride in dimethylformamide, followed by addition of methanesulfonyl chloride at 0° (eq. 54).



(54)

Table VI

Reduction of Ethyl β-butyl(phenyl)thiocrotonates

	Substrate[a]	Reagent	Molar Ration Reagent:Substrate	Solvent	Temp. °C	Time of Reaction, h	Product[b]	Yield[c]
1	A	LAH	1:1	THF	-20°	1	A'	10%
2	A	DIBAH	2:1	benzene	25°	2.5	A'	25%
3	A	DIBAH	2.3:1	ether	25°	1.5	A'	45%
4	A	DIBAH	2.3:1	THF	10-25°	1.5	A'	69%
5	B	DIBAH	2.1:1	THF	10-25°	1.5	B'	70%
6	A	AlH_3	2.1:1	ether	25°	1.5	A'	80%
7	A	AlH_3	2.1:1	THF	10-25°	1.5	A'	93%
8	B	AlH_3	2.1:1	THF	10-25°	1.5	B'	95-97%

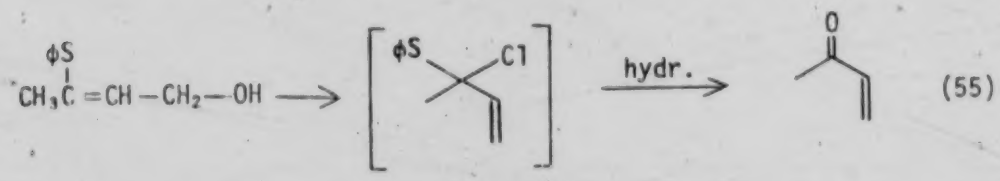
a) A = $\phi S-\underset{\underset{CH_3}{|}}{C}=CH-CO_2Et$, B = $n\text{-}BuS-\underset{\underset{CH_3}{|}}{C}=CH-CO_2Et$

b) A' = $\phi S-\underset{\underset{CH_3}{|}}{C}=CH-CH_2-OH$, B' = $n\text{-}BuS-\underset{\underset{CH_3}{|}}{C}=CH-CH_2-OH$

c) by glc analysis

In our system, however, this approach was unsuccessful. The infrared spectrum of the crude mixture lacked absorption at 1255 cm^{-1} (diagnostic of γ,γ-disubstituted allylic chlorides[121]) and had absorptions at 1715 cm^{-1} and 1680 cm^{-1} (possibly MVK and 4-chloro-2-butanone) and 925 and 975 cm^{-1} (vinyl). The nmr spectrum also confirmed the absence of the anticipated allylic halide (no methylene absorption in the δ 4.3-4.0 region).

This suggested that the rearranged tertiary halide had formed, and by-products like MVK (and 4-chloro-2-butanone) could derive from hydrolysis of the tert-halide during work-up (eq. 55).

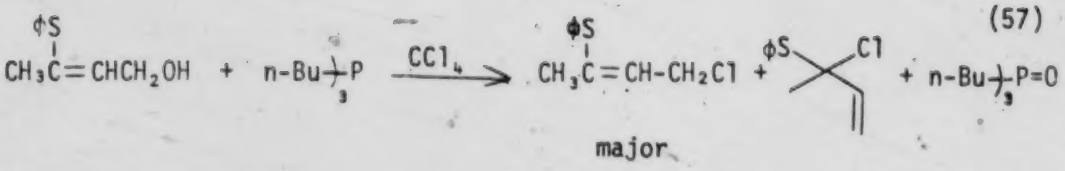


(55)

The next attempt involved reaction of tri-n-butylphosphine with a carbon tetrachloride solution of the allylic alcohol.[107-109,124] These conditions have been used to convert a variety of primary, secondary and allylic alcohols to halides without allylic transposition (eq. 56). In our system, however, this produced a mixture of products

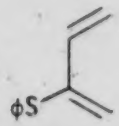
$$R_3P + CCl_4 + ROH \longrightarrow R'Cl + R_3PO + HCCl_3 \qquad (56)$$

of which the primary allylic halide was the major component (eq. 57). The ir spectrum showed absorption at 1255 cm^{-1} (diagnostic of γ,γ-disubstituted allylic chloride)[121] but the small band at 925 cm^{-1} and the shoulder at 1645 cm^{-1} indicated the presence of traces of tertiary



(57)

chloride. The nmr spectrum ($CDCl_3$) showed absorptions for a vinyl methyl as a broad singlet at δ 1.83, a methylene group as two sets of doublets at δ 4.05 and δ 4.35 with J = 7.5 Hz (mixture of E and Z isomers) and vinyl proton absorption as a multiplet (two overlapping triplets) at δ 5.4-6.1. Removal of the by-product, tri-n-butylphosphine oxide, by trituration with pentane (-78°), and filtration proved difficult, and the crude mixture was sensitive to heat or column chromatography. Distillation (Kugelrohr, b.p. 72-78/0.025 mm) produced diene 64 in low yield (ca 30%). The nmr spectrum showed only



64

aromatic and olefinic proton absorptions at δ 7.35 (m, 5H), 6.68 and 6.35 (d, J = 10 Hz, 2H), 5.85 to 5.08 (M, 3H) and the mass spectrum showed a molecular ion of 162 (calcd. 162).

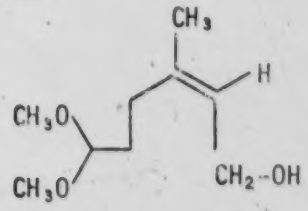
Tris(dimethylamino)phosphine has also been used for this purpose[109], and has the advantage that the by-product, HMPA, is water soluble and thus easily removed during work-up. However, this reagent combination proved too reactive in our system. Reaction of 3-phenylthio-2-butanol with tris(dimethylamino)phosphine in carbon tetrachloride at -20 was very exothermic and resulted in a complex mixture of products.

The use of thionyl chloride as the halogenating agent was next investigated. Young[110] has shown that reaction of γ-methylallyl alcohol with thionyl chloride in dilute ether solution gives exclusively the secondary allylic chloride (eq. 58). In the presence

$$Me-CH=CH-CH_2-OH + SOCl_2 \xrightarrow{ether} Me-\underset{Cl}{CH}-CH=CH_2 \quad (58)$$

(100%)

of tri-n-butylamine, however, a mixture of the α- and γ-methylallyl chlorides is formed. Similarly, γ,γ-disubstituted allylic alcohols, for example 65,[111] undergo allylic transposition to an appreciable extent when subjected to thionyl chloride in the presence of tributylamine.

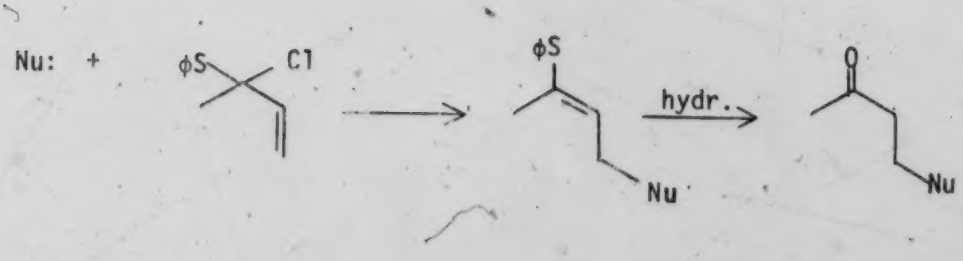


65

On this basis it was anticipated that thionyl chloride would transform allylic alcohol 54 into 3-chloro-3-phenylthio-1-butene, the rearranged tert-halide. This compound could also conceivably serve as an exobutyl equivalent by undergoing nucleophilic substitution via an S_N2' type mechanism[112,113] according to scheme VI.

However, the reaction of 3-phenylthio-2-butanol with thionyl chloride in ether resulted in formation of a mixture of products

Scheme VI



of which the primary halide was the major component. Repetition of this reaction in the presence of one equivalent of tri-n-butylamine produced the primary halide as the sole product in excellent yields (eq. 58).

$$CH_3-\overset{RS}{\overset{|}{C}}=CH-CH_2-OH \xrightarrow[\text{ether}]{SOCl_2/n\text{-}Bu_3N} CH_3-\overset{RS}{\overset{|}{C}}=CH-CH_2-Cl \quad (58)$$

(R = φ, n-Bu, 85-95%)

Thus, the conversion of ethyl acetoacetate to γ-phenyl(n-butyl)-thiocrotyl chloride was accomplished in three facile steps in an overall 50% yield. These halides were utilized as alkylating agents toward various cyclohexanones, as described in the following chapter.

A Study on the Alkylation of Cyclohexanones with γ-phenyl(n-butyl)-thiocrotyl chloride

The annelation of cyclohexanone derivatives with MVK or various β-ketoalkyl equivalents is an important route to fused polycyclic systems. Generally, in any annelation scheme involving a "masked" ketoalkyl halide, one has to deal first with the regioselectivity of the alkylation step. Marshall[17], for example, was confronted with this problem in the alkylation of 2-methylcyclohexanone with 1,3-dichloro-2-butene (DCB) using sodamide in benzene. This approach led to a mixture containing 80% of the 2,2-isomer and 20% of the 2,6-isomer (eq. 41). Evidently, sodium enolates undergo rapid proton transfer, and are unsuitable for alkylation of unsymmetrical ketones.[114] Lithium enolates, on the other hand, undergo a relatively slow equilibration, rendering them more useful for regiospecific alkylations.[32,114]

Initially, the alkylation of a symmetrically substituted ketone, 2,6-dimethylcyclohexanone was studied in order to establish appropriate reaction conditions. Being aware that the hydrolysis of the vinyl sulfide group of the monoalkylated ketone may possibly pose difficulties,[115] the alkylation reaction was investigated with both an aryl- and alkylthio halide: γ-phenylthiocrotyl chloride and γ-n-butylthiocrotyl chloride. The lithium enolate was generated in DME at ca 0° using lithium diisopropylamide as a base following the alkylation procedure recommended by House[35] for the reaction of cyclohexanone with reactive halides (e.g. methyl iodide and benzyl bromide). The enolate solution was then warmed to 30° prior to

addition of the alkylating agent. The course of the alkylation reaction was monitored by glc analysis at time intervals of 30 min, 2 hrs and 10 hrs. It was observed that the alkylation with both halides was much slower in comparison with a reactive halide (benzyl bromide) under identical conditions. For example, while the alkylation with benzyl bromide gave 65% of monoalkylation in 2 min, the reaction with phenyl(n-butyl)thiocrotyl chloride yielded only 45% of the corresponding products in two hours and the reaction was not complete even after 24 hours (63% of phenyl analog, 60% of the n-butyl analog). Evidently, the phenyl(n-butyl)thio unit acts as a deactivating group, resulting in a suppressed reactivity.

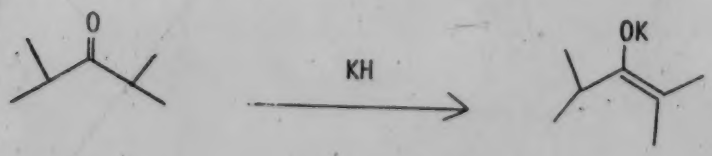
Repetition of the reaction at elevated temperature in order to enhance the rate of alkylation led to a complex mixture of products and reduced the yield of the desired alkylate (Table VII entries 1 and 4).

An alternative way of enhancing the reactivity of the alkylating agent is to use a better leaving group (i.e. I instead of Cl). However, an attempt to prepare γ-phenylthiocrotyl iodide via a Finkelstein reaction merely resulted in appreciable decomposition of starting material. To circumvent this difficulty, the iodide was generated <u>in situ</u>. Thus, the addition of an equivalent of lithium iodide to a solution of the enolate prior to addition of the alkylating agent increased the yield of the monoalkylated product from ca 60 to 70% (Table VII, entries 1, 6). Moreover, 24 hr were required in the case of the chloride to produce a 63% yield, whereas the iodo derivatives gave, after 1 hr, a 73% yield of the desired product.

A similar observation has been made subsequently by Stork[80] and Stotter.[81] For example, allyl chlorides such as γ-chlorotiglates, which were used by Stotter as "masked" ketoalkyl equivalents, were effective alkylating agents for enamines but not for lithium enolates. In contrast, the corresponding iodo analogs gave monoalkylated products in excellent yield either with enamines or lithium enolates.

Since the iodide was considerably more reactive than the chloride, the reaction was repeated at lower temperatures in order to minimize decomposition of the halide. Indeed, at lower temperatures, higher yields of the monoalkylated product could be obtained (Table VII, entries 10-13). Nevertheless, even under the most favourable reaction conditions examined, the crude alkylation mixture always contained varying amounts (up to 10%) of the starting ketone.

Recently, C.A. Brown[82] reported that potassium hydride is exceptionally reactive toward ketones. In ether solvents, potassium hydride vigorously metalates a wide range of ketones with little or no selfcondensation or reduction. For example, 2,4-dimethyl-3-pentanone, when reacted with KH in THF at 20°, formed the potassium enolate in quantitative yield in 10 min (eq. 59).



(59)

Table VII

The alkylation of 2,6-dimethylcyclohexanone with γ-phenyl(n-butyl)thiocrotyl chloride

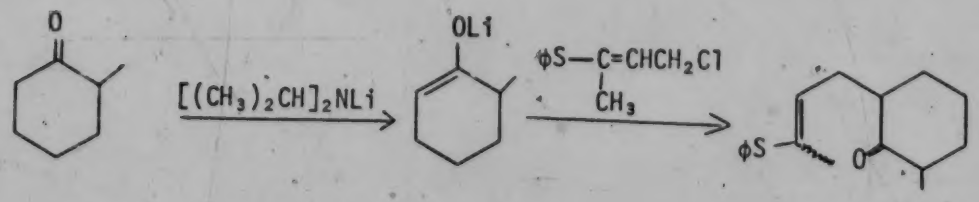
	$RSC(CH_3)=CHCH_2Cl$ R	LiI equiv.	Molar Ratio[a]	Time of reaction (hr)	Temp. (C°)	enolate	solvent	% yield (glc) product	% yield (glc) Recovered ketone
1	φ	-	1.2	24	-5 to 25	Li	DME	63	25
2	φ	-	1.2	1 then 16	30 - 35 25	Li	DME	60	30
3	C_4H_9	-	1.5	1 then 16	25 - 40 45	Li	DME	60	30
4	C_4H_9	-	1.3	1	reflux	Li	THF	<30	_b,c
5	C_4H_9	-	1.3	2 then 0.5	25 reflux	Li	THF	_b	35
6	C_4H_9	1	1.3	1	-5 to 25	Li	DME	71	22
7	C_4H_9	1	2.2	1	40 - 50	Li	DME	<60	_b
8	C_4H_9	-	1.3	16	0	K	THF	45	_b,c
9	C_4H_9	-	1.3	16	0	K[d]	THF	<50	_b,c
10	φ	1	1.3	0.15	-2 to 20	Li	DME	80	10
11	φ	1	1.3	0.50	5 to 25	Li	DME	85	7
12	φ	1	1.3	0.25	-2 to 20	Li	THF	72	15
13	φ	0.5	1.3	0.5	5 to 25	Li	DME	85	8

(a) halide:ketone; (b) was not estimated; (c) complex glc spectra; (d) in the presence of HMPA.

We therefore explored the use of potassium enolates in our system. Since their preparation is much simpler than that of the corresponding lithium enolates, and because of their greater reactivity, the alkylation reaction could be carried out at lower temperatures. Surprisingly, however, the reaction of γ-n-butylthiocrotyl chloride with the potassium enolate of 2,6-dimethylcyclohexanone at 0° was even more sluggish than with its lithium analog, and led to a complex mixture of products containing less than 50% of the desired alkylated ketone. Alkylation in the presence of 15% HMPA with n-butylthiocrotyl chloride was even more complex and clearly inferior to the reaction with lithium enolates.

Having established favourable conditions for alkylation of 2,6-dimethylcyclohexanone, the reaction with an unsymmetrical case was investigated. 2-Methylcyclohexanone was used as a model, in an attempt to independently alkylate at either of the two α positions.

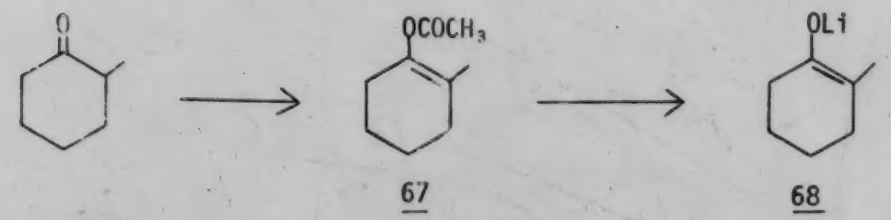
The enolate of the less substituted α-site was easily prepared under conditions of kinetic control with lithium diisopropyl amide as a base.[33] The addition of γ-phenylthiocrotyl chloride to the enolate in DME (with LiI present) afforded the monoalkylated product 66 in 85 - 87% yield (eq. 60).



(60)

66

The positional isomer 68 was prepared by first transforming the ketone into enol acetate 67 which in turn was treated with methyllithium as base. The alkylation proceeded smoothly and an 85% yield of the desired product was obtained (eq. 61).



67 68 (61)

68 69 (85%)

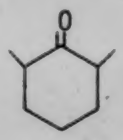
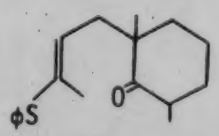
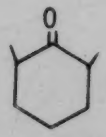
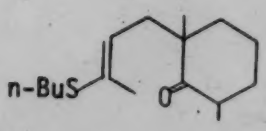
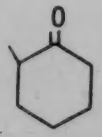
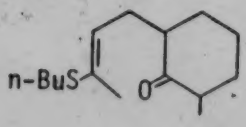
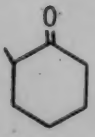
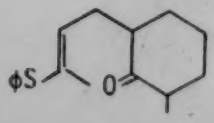
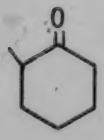
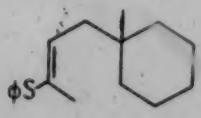
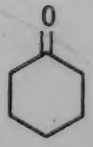
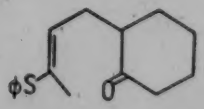
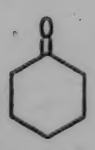
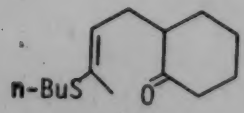
The results for various ketones are summarized in Table VIII.

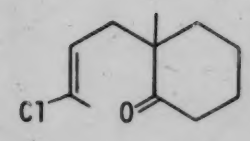
The NMR spectrum ($CDCl_3$, 100 MHz) of 69 indicates, as expected, that the product is a mixture of cis and trans isomers. The angular methyl group appears as two sharp singlets at δ 1.10 and δ 1.08, and the vinyl protons at δ 5.84 - 5.62 show as two overlapping triplets. The remaining adsorptions are: δ 1.9 - 1.6 (m, 8H) methylene protons; broad singlet at 1.95 for vinyl methyl protons; the allylic absorption appears as a broad doublet at 2.5 - 2.27 (J = 6 Hz), and the aromatic protons exhibit absorption at δ 7.3.

In similar systems which contain one isomer only, the angular methyl appears as a singlet. For example, compound 70[17,62] (prepared from Z-1,3-dichloro-2-butene) exhibits methyl absorption at δ 1.07 as

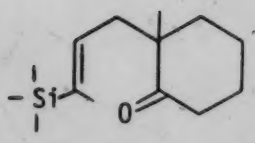
Table VIII

Preparation of 2-[γ-phenylthiocrotyl]cyclohexanones

	$RSC(CH_3)=CHCH_2Cl$ R	Ketone	Product	glc yield	isolated yield
(1)	C_6H_5			85 - 87%	80%
(2)	C_4H_9			83 - 85%	75%
(3)	C_4H_9			80%	72%
(4)	C_6H_5			85%	75%
(5)	C_6H_5			87 - 90%	80%
(6)	C_6H_5			75%	68%
(7)	C_4H_9			78%	70%



70



71

a singlet. Analagously, the angular methyl of 80 appears as a singlet at δ 0.98.

In the NMR spectrum of 66 ($CDCl_3$, 100 MHz) the absorption of the 6-methyl group appears as two doublets at δ 1.15 - 1.07 and 1.07 - 1.00 with J = 6.5 Hz. The presence of the two doublets is probably due to the cis and trans configuration of the double bond. A similar situation was observed in 69 where the angular methyl appears as two sharp singlets instead of one. The remaining NMR absorptions were consistent with the proposed structure.

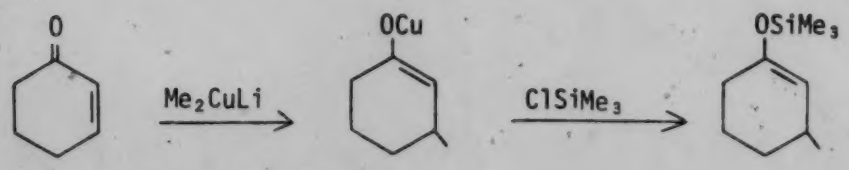
In an attempt to extend the scope of the alkylation reaction, a brief study was conducted on the alkylation of copper enolates.

Conjugate addition of organocopper reagents to 2-cycloalkenones leads to a specific enolate which is regiochemically stable. Recently, these intermediates have been successfully alkylated with several reactive halides (methyl iodide, benzyl bromide, allyl chlorides, etc.)[116-119] and were also shown to undergo regiospecific Michael reactions with α-silyl-MVK derivatives.[73,74,75]

In the present study the copper enolate was prepared by the conjugate addition of lithium dimethyl cuprate or polymeric methyl copper (I) to 2-cyclohexenone. Attempts were made to trap this

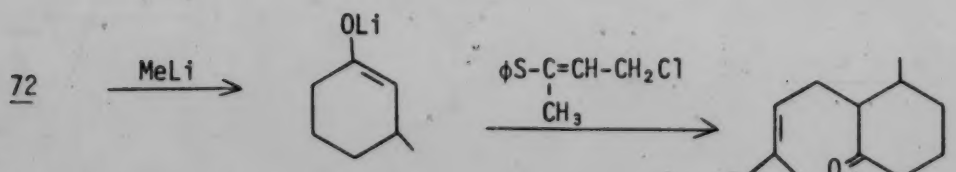
enolate with γ-phenyl(n-butyl)thiocrotyl chloride in ether, DME, or THF-HMPA solvent systems. In all these trials a complex mixture of products resulted in which the desired compound was obtained in less than 30% yield. Moreover, attempts to activate the system by employing complexing agents like dimethyl sulfide or excess lithium iodide proved ineffective. Apparently copper enolates are insufficiently reactive toward the thiocrotyl halide system.

One way of potentially circumventing this lack of reactivity is to trap the initially generated copper enolate as a trimethylsilyl enol ether,[117] and subsequently regenerate the more reactive lithium enolate from this derivative.[33,127] If successful, the scope of the alkylation would be extended beyond those cases in which only α- or α,α'-substituents flank the carbonyl. Thus, conjugate addition of lithium dimethyl cuprate to cyclohexenone, followed by quenching with trimethylsilyl chloride produced enol silyl ether 72 in 77% yield (eq. 62). The lithium enolate was generated by treatment with



(62)

72



73

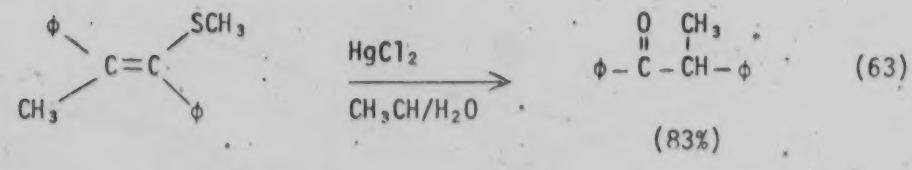
74

methyllithium and this was alkylated (under conditions established previously) with γ-phenylthiocrotyl chloride. This afforded 2-[γ-phenylthiocrotyl]-3-methylcyclohexanone in 90% yield.

Having accomplished the alkylation of several representative ketones, we were left with the final task of "unmasking" the carbonyl group and cyclization of the dicarbonyl system to the desired octalones.

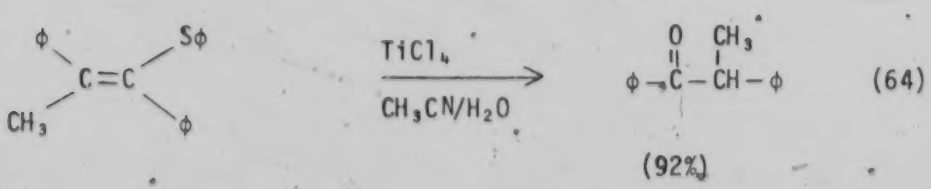
A Study on the Hydrolysis of 2-[γ-phenyl(n-butyl)thiocrotyl]cyclohexanone derivatives

The hydrolysis of vinyl sulfides to ketones has usually been effected under rather drastic acidic conditions.[88,89] Recently, however, two mild hydrolysis procedures have been reported. Corey and Shulman[83] have shown that mercuric chloride in aqueous acetonitrile affords high yields of pure ketone (eq. 63), and subsequently, Mukaiyama and co-workers[82] have shown that titanium tetrachloride in



(63)

various solvent systems readily hydrolyzes vinyl sulfides to the corresponding ketones in high yields (eq. 64).



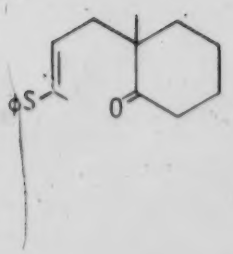
(64)

Strong acid was to be avoided in our system, since analogous 1,5-dicarbonyl systems are known to preferentially cyclize to undesired bridged bicyclics.[17,124] Therefore several mild hydrolysis procedures were investigated.

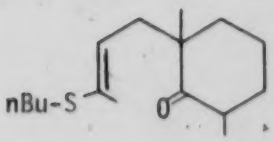
Mercuric chloride produces two equivalents of hydrochloric acid during the hydrolysis of vinyl sulfides. In order to decrease the acidity of the media, the reaction of 2,6-dimethyl-2-[γ-phenylthiocrotyl]cyclohexanone with $HgCl_2$ was attempted in the presence of bases[125] and thiol scavengers such as: mercuric oxide, cadmium carbonate, and calcium carbonate. However, all these combinations of reagents proved entirely ineffective. Similarly, addition of "proton sponge", 1,8-bis-(dimethylamino)naphthalene, was without effect. No reaction took place even after refluxing for prolonged periods of time, and in all these attempts the starting materials were recovered quantitatively.

Even without additives, the phenyl vinyl sulfide, when treated with mercuric chloride in aqueous acetonitrile, failed to undergo hydrolysis after 40 hr at reflux temperature (eq. 65). Similarly, 2-methyl-2-(γ-phenylthiocrotyl)cyclohexanone remained unchanged under these conditions.

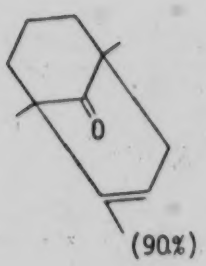
In contrast to the above observations with the phenylthio derivative, the n-butylthio analog of 2,6-dimethylcyclohexanone was hydrolyzed in excellent yield using mercuric chloride in aqueous acetonitrile (room temperature, 40 hr). Instead of the anticipated dicarbonyl compound, however, the bridged bicyclic, 1,2,5-trimethylbicyclo[3.3.1]non-2-en-9-one, was isolated in 90% yield (eq. 66). Interestingly, mercuric chloride-aqueous acetonitrile failed to hydrolyze this vinyl sulfide when one equivalent of calcium carbonate was added.



$HgCl_2$, CH_3CN-H_2O → N.R. (65)

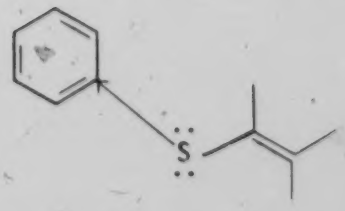


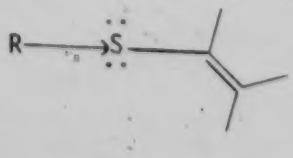
$HgCl_2$, CH_3CN-H_2O →



(90%) (66)

The dramatic difference in reactivity between the phenyl and the n-butyl analog may be the result of the diminished basicity of sulfur in the phenyl derivative due to electronic effects (inductive and/or resonance).



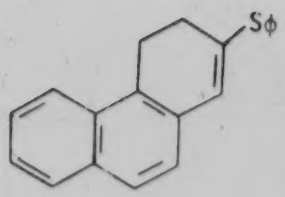


However, it is known that certain phenyl vinyl sulfides hydrolyze with $HgCl_2$ whereas others do not. For example, Trost and co-workers[115] have observed that whereas compound 75 was readily hydrolyzed with

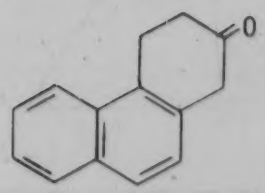
mercuric chloride in hot aqueous acetonitrile (eq. 67), compound 76 was not. Apparently, rather subtle factors are operative, requiring different methods to achieve hydrolysis. Compound 76, for example, could be hydrolyzed with $TiCl_4$ (eq. 68).

$$\underset{\underset{\phi S}{|}}{\phi CH=C-CH_3} \xrightarrow{HgCl_2} \underset{}{\overset{O}{\overset{\|}{\phi CH_2CCH_3}}} \qquad (67)$$

75 (85%)



$$\xrightarrow{TiCl_4}$$



(68)

76

Mercuric chloride has been shown to hydrolyze both thioacetals and vinyl sulfides.[83,125] This prompted an examination of several reagents which were also shown to be effective for the hydrolysis of thioacetals, in anticipation that they may hydrolyze vinyl sulfides as well. Thus, the hydrolysis of both the phenyl and n-butylthiocrotyl derivatives of 2,6-dimethylcyclohexanone was attempted with: copper (II) chloride - copper oxide in refluxing acetone,[126] mercuric oxide - boron trifluoride in THF,[127] and ceric ammonium nitrate in aqueous acetonitrile.[128] However, these reagents were

found unsuitable for our system. With the first two reagent combinations, the starting material remained unchanged and was recovered quantitatively, and with ceric ammonium nitrate a complex mixture of products resulted in which the derived diketone was formed in less than 5% yield (glc analysis).

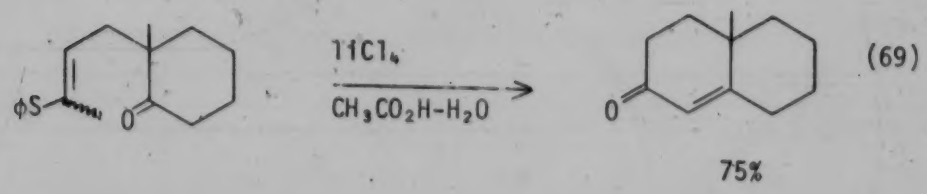
Subsequently, the titanium tetrachloride-promoted hydrolysis was investigated.[82] In this procedure the vinyl sulfide is initially treated with two equivalents of titanium tetrachloride at room temperature and this is followed by addition of water (4 equiv.). The reaction can be carried out successfully in three different solvents: acetonitrile, methylene chloride, and acetic acid. In certain cases the addition of one equivalent of lead hydroxide (to remove thiol) has been found to increase yields.[82]

Initial results with this procedure were rather disappointing. For example, the reaction of 2-methyl-2-(γ-phenylthiocrotyl)cyclohexanone with titanium tetrachloride in either methylene chloride or acetonitrile resulted in a mixture of several products as determined by glc analysis. Addition of lead hydroxide did not improve the outcome of the reaction.

However, in acetic acid the reaction was complete in less than thirty minutes and glc analysis indicated the formation of one major product (75% yield). The infrared spectrum of the crude mixture showed no evidence of the anticipated dicarbonyl compound. Instead, there were absorptions at 1680 and 1620 cm^{-1} (characteristic of a conjugated enone), and glc-mass spectral analysis of the major component indicated a molecular weight of 164. This product was isolated by

column chromatography on silica gel (elution with heptane-methylene chloride), and its nmr spectrum proved to be identical with that of an authentic sample* of 10-methyl-$\Delta^{1,9}$-octal-2-one, prepared by the Heathcock and Ellies[76] annelation reaction.

This interesting observation suggested that an *in situ* hydrolysis-cyclization reaction was being effected by $TiCl_4$, and moreover, the cyclization was being directed predominantly, if not exclusively, to the desired octalone (eq. 69).



(69)

75%

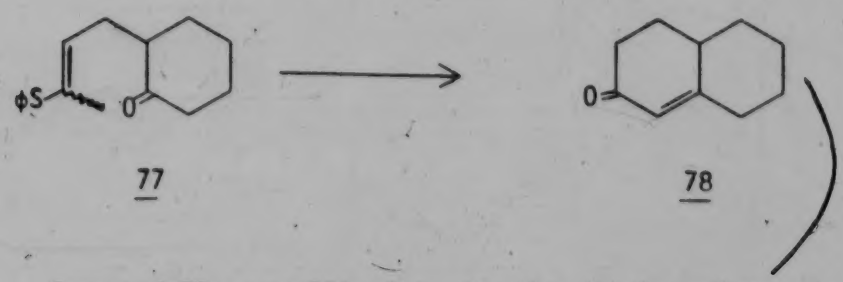
The reaction of tin tetrachloride was also examined with the above compound since tin tetrachloride has certain resemblances to titanium tetrachloride. For example, the estimated ionic radii (Sn^{4+}=0.71Å, Ti^{4+}=0.68Å) are similar,[129] and tin tetrachloride, like titanium tetrachloride, is a distillable liquid which behaves as a typical Lewis acid, giving adducts with Lewis donors. However, the reaction of tin tetrachloride with 2-methyl-2-(γ-phenylthiocrotyl)-cyclohexanone in either methylene chloride or acetic acid proved more sluggish than that of titanium tetrachloride, and the yield of the desired octalone was considerably lower (ca 35-40% glc yield).

---

* A sample of this compound was kindly provided by Dr. L.M. Browne.

As a result of these trial experiments with various reagent combinations, the $TiCl_4$ method clearly proved to be the most promising. Further efforts of hydrolysis were therefore concentrated on the $TiCl_4$ system with the various alkylation products described previously.

Thus, 2-(γ-phenylthiocrotyl)cyclohexanone, 77, underwent smooth hydrolysis with $TiCl_4$ at 65°. The reaction was complete in 60 min and afforded $\Delta^{1,9}$-octalone-2, in 77% yield (eq. 70).



77 78 (70)

Compound 77 crystallized on standing in the refrigerator for several months, (m.p. 142-148°). However, the ir spectrum of the crystalline material showed carbonyl absorption at 1715 cm^{-1}, but no olefinic absorption at 1630 cm^{-1}. The nmr spectrum lacked absorption for a vinyl proton, and exhibited only absorptions for five aromatic protons at δ 7.5 and for fifteen aliphatic protons at δ 1-2.7. The molecular weight was determined by high resolution mass spectroscopy as 260.12353 (calcd. for $C_{16}H_{20}S$: 260.12349), which is the same as that of the starting material, 77. A comparison of the mass spectrum of authenic compound 77 and the crystalline product showed major differences in their respective fragmentation patterns and each possessed different base peaks (133 and 151 respectively). On the basis of this spectral data, it is concluded that

77 underwent cyclization in the refrigerator due to traces of acid to afford compound 79 which is essentially an adduct of the enone and benzenethiol (eq. 71).

(71)

77 79

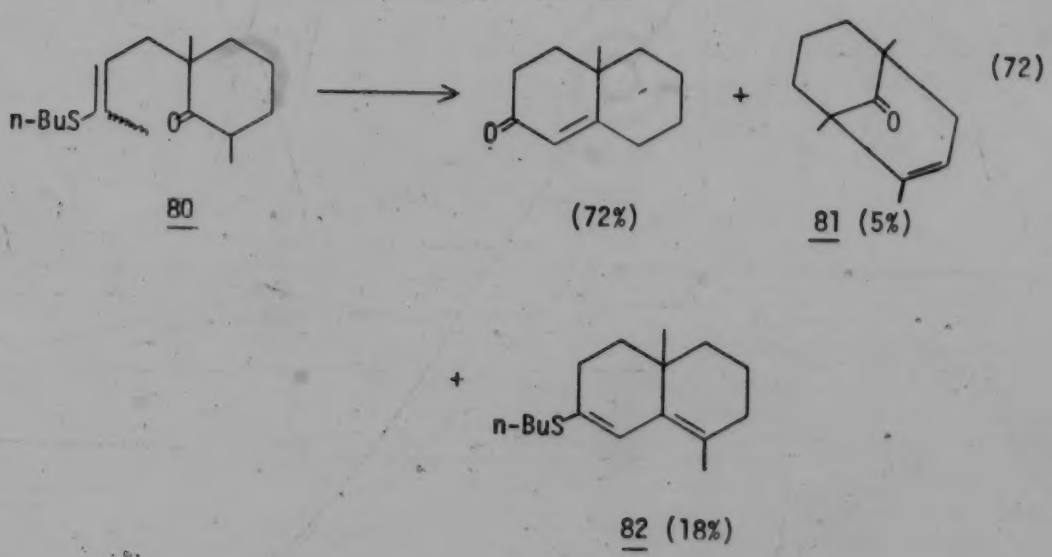
To check[133] if mild acidic conditions could effectively hydrolyze vinyl sulfide alkylates, two substrates were selected for trial: the 2,6-dimethyl- and the 3-methyl analog. However, the former proved unreactive toward refluxing dilute HCl-ethanol, and the 3-methyl analog gave a mixture of the octalone and the bridged bicyclic ketone. Similarly an attempt[133] to hydrolyze the latter compound by absorbing it on acid washed alumina (pH 3) and on 25% silver nitrate on silica gel proved ineffective.

The hydrolysis of the phenyl thiocrotyl alkylate of 2,6-dimethyl cyclohexanone with titanium tetrachloride proved to be troublesome. In contrast with the previous substrates (which cyclized rather readily), the hydrolysis of this analog was incomplete after 16 hr at room temperature. Increasing the temperature resulted in a faster reaction rate, though the yield of the desired octalone was essentially constant, and a new product, 2,6-dimethyl-9-phenyl-thio-bicyclo[4.4.0]-1,9-decadiene appeared (Table IX, entries 1,2).

The use of excess $TiCl_4$ was ineffective at increasing the yield of octalone (Table IX, entry 4).

On the other hand, the n-butylthio analog proved more susceptible to hydrolysis. The reaction of the 2,6-dimethyl analog with $TiCl_4$ was complete in a relatively shorter time period (4 hr 40°) and the yield was improved (Table IX, entry 7).

In addition to the desired octalone, two other products were detected by glc, isolated, and characterized as the bridged bicyclic compound 81 and vinyl sulfide 82 (eq. 72).



80 → (72%) + 81 (5%) + 82 (18%) (72)

The structure assignment of thioenol ether 82 was based on the following spectral data: The molecular weight was determined as 250.2044 (calcd. for $C_{16}H_{26}S$: 250.2047) by high resolution mass spectroscopy; the nmr spectrum ($CDCl_3$, 100 MHz) exhibited an olefinic absorption for one proton at δ 6.3; the ir absorption

Table IX

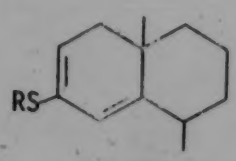
Hydrolysis of 2,6-dimethyl-6-[γ-phenyl(n-butyl)thiocrotyl]cyclohexanones with titanium tetrachloride in acetic acid.

Run	Substrate[a]	$TiCl_4$ (equiv)	H_2O (equiv)	Temp (°C)	Reaction Time (hr)	Starting Material (%)	enone %	Bridged bicyclic (%)	Thioenol ether (%)
1	I	2.2	4.0	R.T.	16	30	60	5	—
2	I	2.2	4.0	85-90	2.5	15	62	3	10
3	I	2.2	5.0[b]	90	3	5	67	8	5
4	I	2.9	4.0	R.T. then 90 for	3 3	17	60	3	13
5	II	2.2	4.0	R.T.	16	7	53	7	22
6	II	2.7	4.0	50	6	—	70	7	11
7	II	2.0	4.0	40	4	—	72	5	18

a. I = the thiophenyl analog, II = the n-butylthio analog.

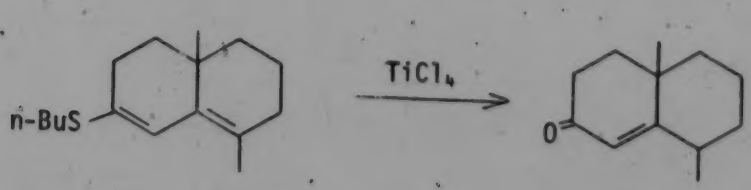
b. 1 equivalent of water was added after 2 hr.

at 1590 cm^{-1} (probably due to a conjugated diene system); and the u.v. spectrum (MeOH) showed a maximum at 277 mμ (ε = 9.150), which is strong indication for a conjugated diene system substituted by an alkylthio group (calcd. λmax 269 mμ). A cross-conjugated structure such as 83 may therefore be excluded.



83

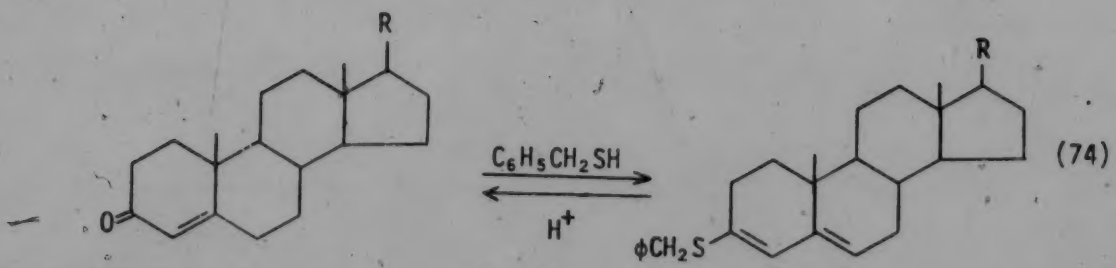
Apparently thioenol ether 82 arose as a consequence of the reaction of the enone with free thiol present in the hydrolyzed reaction mixture. Retreatment of 82 with $TiCl_4$ in acetic acid (r.t. 1 hr) gave the desired octalone in 75% yield (eq. 73).



82 (75%) (73)

Similar observations have also been made in the steroid series. Djerassi and co-workers[130] have found that 3-keto-$\Delta^{4,5}$ steroids can be converted to conjugated thioenol ethers with benzylmercaptan in the presence of pyridine hydrochloride as a catalyst (eq. 74). Compound 84 (R = $COCH_3$, $COCH_2OAc$, O, OH, C_8H_{17}) shows an ultraviolet

maximum (dioxane) at 268 mμ, which is similar to that obtained for compound 82.



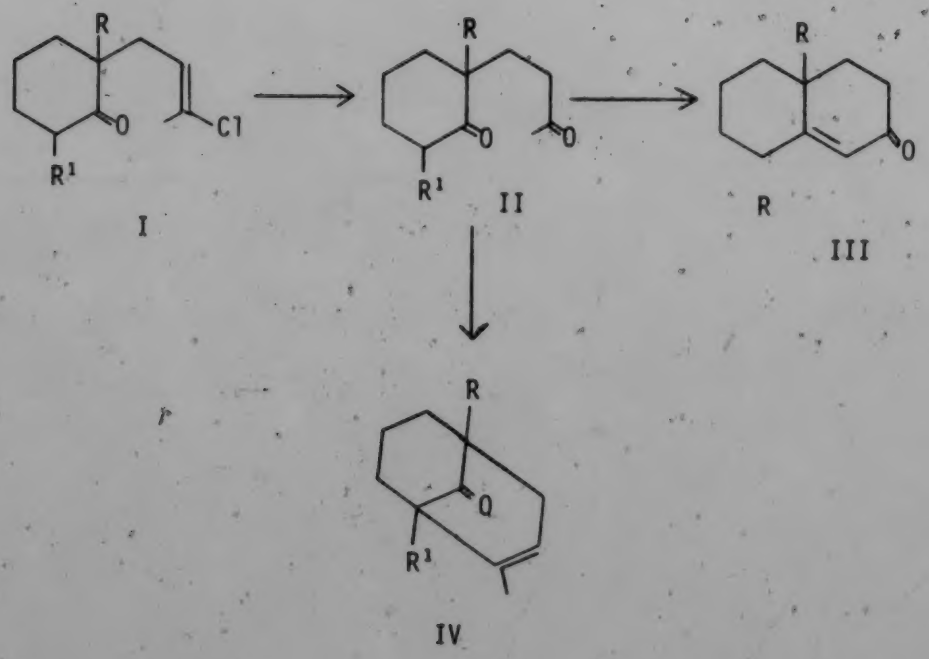
(74)

84

In an attempt to circumvent the formation of by-product 82, the hydrolysis was also carried out in the presence of mercuric oxide (a thiol "scavenger"). However, this modification led to extensive decomposition and only ca 10-15% yields of bicyclic enone resulted.

The formation of the bridged bicyclic ketone 81 in 5% yield is in sharp contrast to Marshall's results[17] and to our observations of the hydrolysis of vinyl sulfide 80 with mercuric chloride in aqueous acetonitrile. In both these cases, the undesired bridged bicyclic isomer is the exclusive product.

Marshall and Schaeffer noted that all three γ-chlorocrotyl-cyclohexanones, I_a, I_b, and I_c, upon treatment with conc. sulfuric acid at 0°, show a preference for cyclization to bridged bicyclo-[3.3.1]nonanone systems IV_a, IV_b, and IV_c, over octalones II_a, II_b, and II_c (eq. 75).



I II III IV

a. $R = CH_3$; $R^1 = H$
b. $R = H$; $R^1 = CH_3$
c. $R = R^1 = CH_3$
d. $R = R^1 = H$

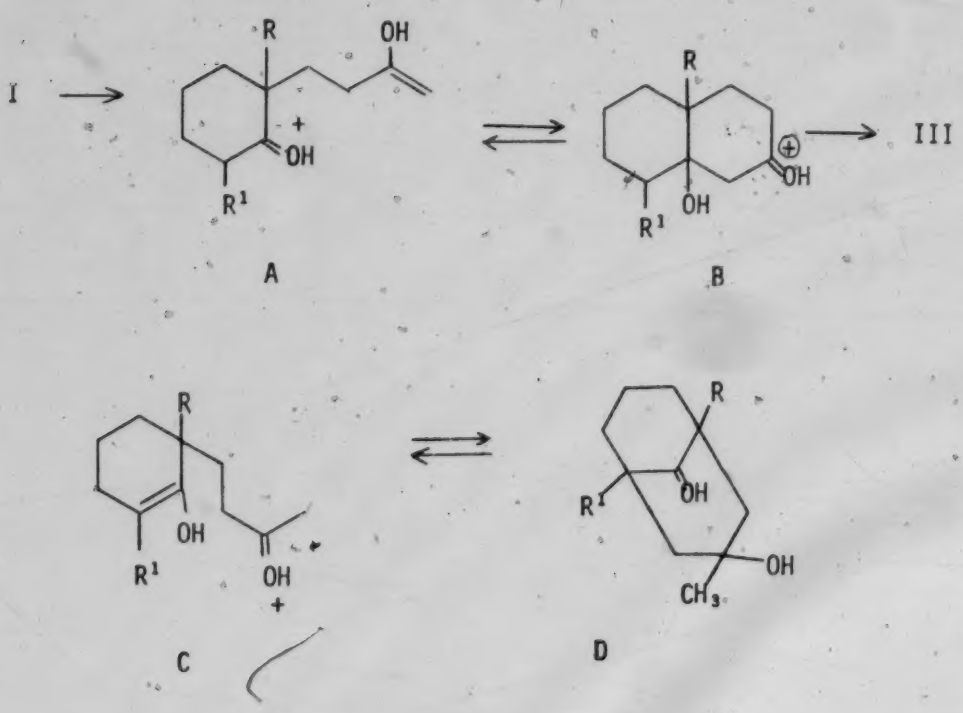
For example, hydrolysis of Ia afforded in 58% yield a mixture (85:15) of dione IIa and bridged ketone IVa; similarly, hydrolysis of Iv gave a mixture (87:13) of dione IIb and bridged ketone IVb in 61% yield and no octalone could be detected. Hydrolysis of IIIa, however, produced exclusively the undesired bridged ketone IVc in 93% yield.

These findings provide an interesting contrast with the results obtained by Julia[124] on the hydrolysis of 2-(γ-chlorocrotyl)cyclohexanone, Id. In this case a mixture was formed in which the

bicyclo[4.4.0] and the bicyclo[3.3.1] products were formed in nearly equal amounts.

Marshall has suggested that two factors control the direction of the cyclization reaction (scheme VII): the steric environment of the cyclohexanone carbonyl grouping, and the difference in stability of the enols A and C (due to hyperconjugative stabilization).

Scheme VII

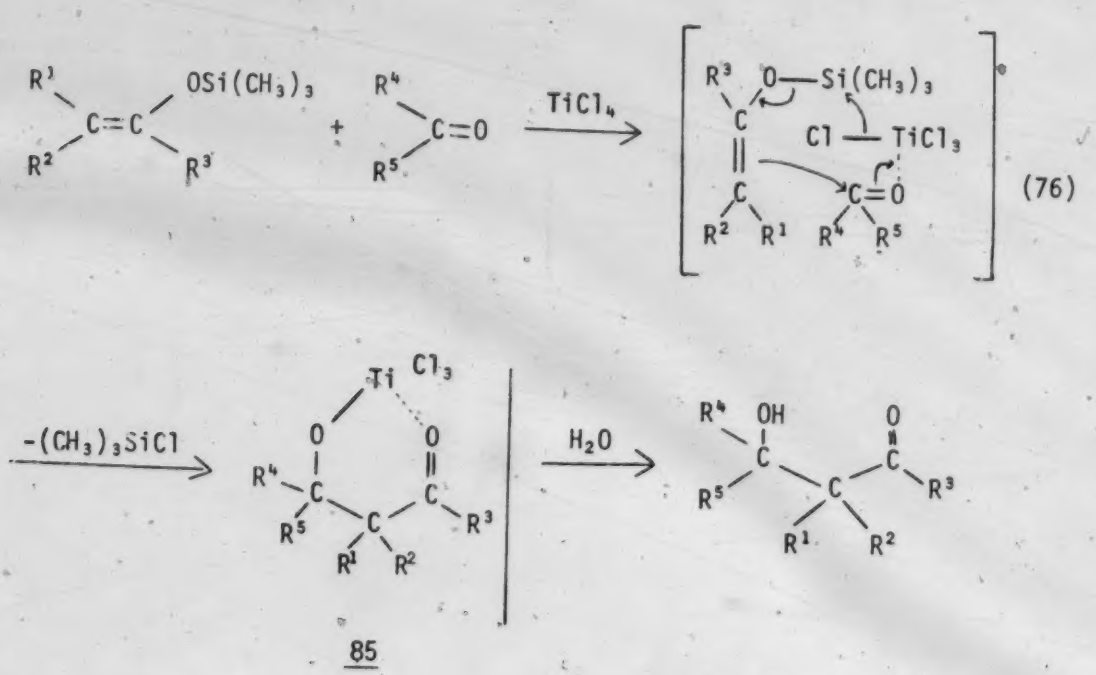


a, $R = CH_3$; $R^1 = H$

b, $R = H$; $R^1 = CH_3$

c, $R = R^1 = CH_3$

Thus, it is suggested that methyl groups in the 2- and 6-position on the cyclohexanone ring should retard the reaction A ↛ B. On the other hand, both a 2- and 6-methyl group might be expected to facilitate the reaction leading to the bicyclo[3.3.1] product (C → D). The energy difference between the conformer with an axial butanone side chain (needed for the formation of bridged product Da) and the equatorial side-chain conformer (where bridging is prohibited by steric effects) should be smaller in the 2-methyl-2-(3-oxobutyl)cyclohexanone intermediate Ca than in the corresponding desmethyl analog C (R = R^1 = H) where the equatorial side chain should be greatly favored. Bridged product IV might therefore be more easily formed.

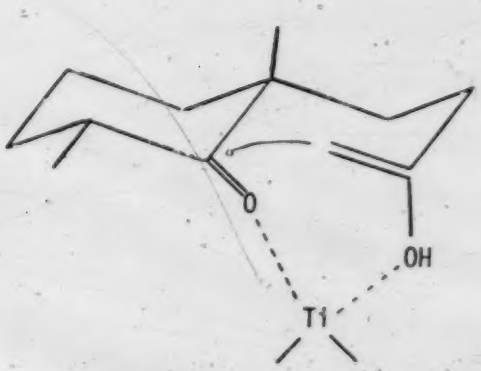


(76)

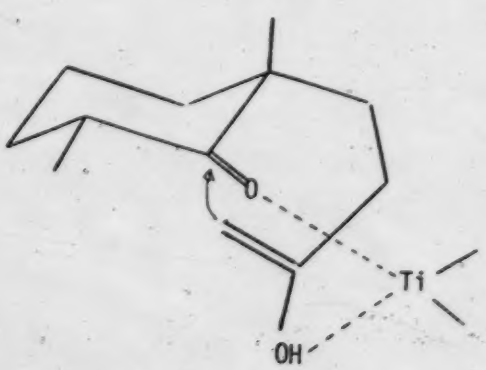
85

The difference between Marshall's results and ours is undoubtedly due to the role electrophilic titanium plays in our system. Mukaiyama[131], for example, has shown that in crossed-aldol reactions, titanium tetrachloride strongly activates the reaction of silyl enol ethers with carbonyl compounds (eq. 76), and suggests that formation of chelate 85 is a strong driving force for the formation of the aldol product. Similarly, House[132] observed that the addition of divalent metal salts such as $MgBr_2$ or especially $ZnCl_2$ to preformed lithium enolates, followed by treatment with aldehydes results in formation of a single aldol product in 80-90% yields. Again, this has been explained by the formation of a metal chelate which probably assisted in displacing the equilibrium reaction in favor of aldol formation.

Thus, the driving force in the $TiCl_4$-promoted cyclization to the bicyclic[4.4.0]decanone system is most reasonably attributed to formation of the intermediate, six-membered cyclic titanium chelate, E and/or F. For the formation of the bridged bicyclic compound, the 2-butanone side chain of the dione IIc has to be in the axial position. There are two important conformers of the

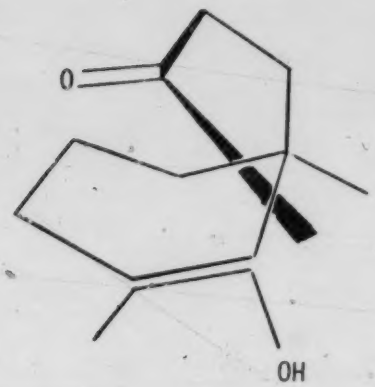


E

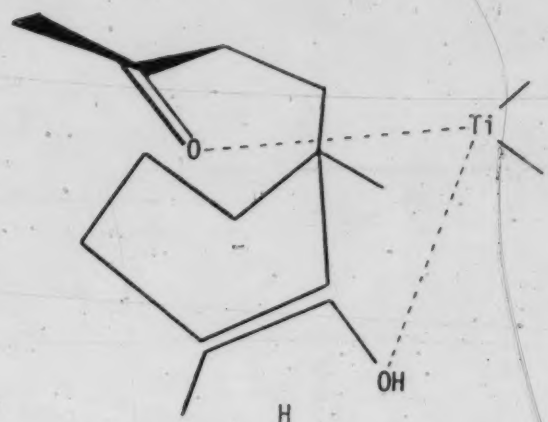


F

side chain to be considered. Inspection of Dreiding molecular models shows that in conformer H the plane of the carbonyl group almost bisects the plane of the enol double bond, thus preventing



G



H

efficient overlap of the two π systems. However, the carbonyl and hydroxyl groups are favorably disposed for chelation to titanium. In conformer G, on the other hand, the two π systems may lie in the same plane suitably disposed for overlap. This may facilitate C-C bond formation, but the carbonyl and the hydroxyl group are now too far apart for effective chelation to occur.

In Dreiding models of intermediates E and F, however, both efficient π-overlap and reasonable bridging distance (for Ti chelation) can occur.

This additional stabilization in conformers E and F due to chelate formation probably offsets the steric retardation mentioned by Marshall,[17] and results in preferential formation of the octalone.

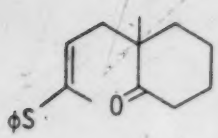
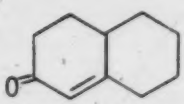
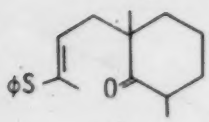
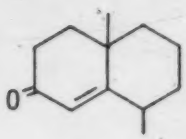
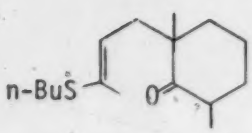
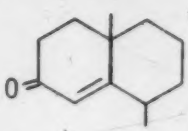
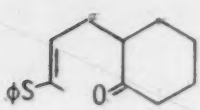
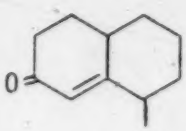
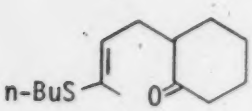
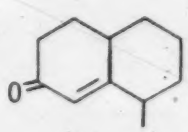
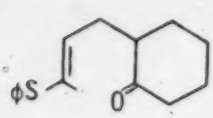
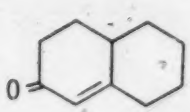
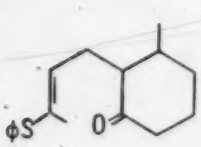
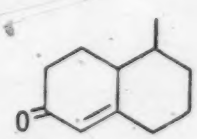
However, the flexibility of Dreiding models of such systems cannot permit a clear choice between conformer E and F. New C-C bond formation from conformer E (equatorial attack) would lead to a trans-decalin system, whereas conformer F (axial attack) would produce a cis decalin. House has argued that the usual "axial attack" observed in kinetically controlled alkylation of enolates is substantially diminished in the presence of chelating agents (Zn^{++}).[132] In the latter, the outcome is predominant equilibrium control (i.e., increased equatorial attack). However, this point cannot be resolved in our system, since in none of the cyclization experiments could any intermediate ketol (or dione) be detected.

Hydrolysis-cyclization of the cyclohexanone alkylate behaved similarly to the 2,6-dimethyl analog toward titanium tetrachloride. The phenylthio derivative underwent slow reaction and was incomplete after 10 hr at 50°. The n-butylthio analog, however, underwent relatively fast hydrolysis-cyclization (4 hr, 50°) and afforded the corresponding octalone in 73% yield (Table X, entries 4,5).

Interestingly, the acid-catalyzed hydrolysis of 2,6-dimethyl-2-(γ-chlorocrotyl)cyclohexanone occurs markedly faster than the analogous reaction of the monomethyl compounds (Ia, Ib). However, in the $TiCl_4$-promoted hydrolysis of the analogous vinyl sulfides, the 2,6-dimethyl analog hydrolyses much slower than the less substituted derivatives. Thus, the qualitative rates of the hydrolysis decrease in the following order: 2-methyl > unsubstituted > 6-methyl > 2,6-dimethylcyclohexanone alkylate (similarly, in the n-butyl vinyl sulfide series the rate decreased in the order: unsubstituted > 6-methyl > 2,6-dimethylcyclohexanone alkylate).

Table X

The reaction of 2-[γ-phenyl(n-butyl)thiocrotyl]cyclohexanone derivatives with titanium tetrachloride

	Substrate	Enone	glc yield	isolated yield
1			75%	63%
2			67%	-
3			72%	59%
4			65%	-
5			73%	63%
6			77%	65%
7			73%	-

Again, this may be explained on the basis of steric retardation and enol stabilization on the one hand, and the chelation effect of titanium on the other.

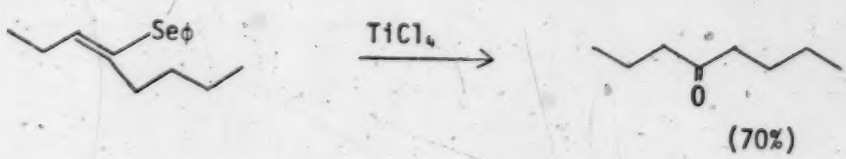
In the cyclization of conformer E, for example, the oxobutyl side chain is held in the equatorial position due to Ti chelation. However, the side chain may be subjected to steric interaction with the methyl in the 2- and 6-position of the cyclohexanone ring. As a result the cyclization of the 2,6-dimethyl analog is expected to be the slowest in this series. On the other hand, in the reaction of the chlorocrotyl analog leading to the bridged bicyclic ketone, the oxobutyl side chain (in the axial position) encounters less steric interaction.[17] Moreover, since the endocyclic enol Cc of the 2,6-dimethyl alkylate is more stable than analog Ca (due to hyperconjugative effects) it is observed to cyclize faster.

In conclusion, titanium tetrachloride in acetic acid was found to be very effective for the hydrolysis and cyclization of vinyl sulfides.*

The hydrolysis of 2-[γ-phenyl(n-butyl)thiocrotyl]cyclohexanone derivatives concludes the scheme for the preparation of octalones. Although the yields of the hydrolysis reaction are in the vicinity of 60%, the reaction holds a particular place of importance. Whereas other existing methods obtain these products after lengthy multi-step

---

* Interestingly, this reagent combination has recently been observed by Dr. Mortimer[134] to hydrolyze vinyl selenides instantaneously in good yield.



(70%)

procedures, the present scheme succeeds in preparing difficulty obtainable octalones (like 8,10-dimethyl-1(9)-octal-2-one) in two facile steps from the starting ketone.

EXPERIMENTAL

General Considerations

Infrared (ir) spectra were recorded on an Unicam SP1000 Infrared Spectrophotometer. Nuclear magnetic resonance (nmr) spectra were run on a Varian A-60 or HR-100 spectrometer. Unless otherwise stated, deuterated chloroform ($CDCl_3$) was employed as the solvent with tetramethylsilane (TMS) as the internal reference standard. Chemical shifts are reported as δ values relative to TMS = 0. The following abbreviations were used in the text: s = singlet, d = doublet, t = triplet, and m = multiplet. Mass spectra were recorded on a AEI Model MS-2 or Model MS-9 spectrometer. Spectra are reported in the following fashion: m/e = peak mass (relative intensity).

Gas liquid chromatography (glc) was performed using an Aerograph A-90-p3 and Varian Aerograph series 1200 gas chromatographs. The following columns were used: Column A: 5'/1/8" 5% SE-30 on chromosorb G-DMCS; column B: 5'/1/8" 5% OF-1 on chromosorb W; column C: 10'/1/8" 15% SE-30 on chromosorb W; column D: 5'/1/8" 20% DEGS on chromosorb W; column E: 5'/1/8" 10% carbowax 20 M on chromosorb W.

Refractive indices were measured on a Bausch and Lomb Abbe-3L Refractometer.

The alkylation and reduction reactions were carried out under an atmosphere of oxygen-free nitrogen.[56]

The concentration of commercial methyllithium in ether (Foote, 1.5-1.6M) was determined by titration with 2-butanol in xylene.[120]

Preparation of ethyl γ-phenyl(n-butyl)thiocrotonate

Ethyl β-chlorocrotonate. This ester was made by a modification of Vernon's method.[90] A suspension of phosphorus pentachloride (418 g, 2 mol) in benzene (300 ml) was kept at 0° with stirring. Ethyl acetoacetate (130 g, 1 mol) was added dropwise during 3 hr. The mixture was stirred at 0° for 24 hr. Ice-cold methanol (300 cc) was added slowly (6 hr), with efficient stirring at 0° to 5°. The reaction mixture was then neutralized with cold saturated solution of sodium hydrogen carbonate (ca 500 ml). The mixture was then extracted with pentane (3 x 200 ml), the organic layer was washed with water, then with brine and dried (Na_2SO_4). After removal of the solvent at atmospheric pressure the crude product was distilled under reduced pressure. This afforded 90 g (62%) of ethyl β-chlorocrotonate (as a mixture of the E and Z isomers) b.p. 48-70°/10 nm; ir (liquid film): 1721 and 1712 (C=O, E and Z), 1637 and 1631 (C=C, E and Z), 1189 (C-O, ester str.), 685 and 658 cm^{-1} (C-Cl str, E and Z isomers); nmr: δ 6.1 (br, s, 1H) $CH_3C(Cl)=CH$, 4.2 (9, J = 7 Hz, 2H) CH_3CHO, 2.6 (d, J = 0.5 Hz, 3H) $CH_3C(Cl)=C$ (Z isomer), 2.25 (d, J = 0.5 Hz, 3H) $CH_3C(Cl)=C$ (E isomer), 1.3 (t, J = 7 Hz, 3H) CH_3CH_2O.

Ethyl β-phenylthiocrotonate (E and Z mixture) Benzenethiol (44 g, 0.4 mol) was added to an ethanol solution (150 ml) containing an equivalent amount of sodium ethoxide (from 9.2 g Na, 0.4 mol) at 0°C. To this solution ethyl β-chlorocrotonate (67.7 g, 0.45 mol) was added dropwise over a period of 15 min at 0° and the reaction mixture was stirred for an additional 2.5 hr, during which time a white precipitate developed. At the end of this period, the mixture was poured into ice cold water (4l) then extracted with ether (5 x 100 ml). The combined ether extracts were reduced in volume and dried ($MgSO_4$). Ether was removed by distillation at atmospheric pressure and the residue was fractionally distilled through an 8 cm Vigreux column at 1.5 mm. This afforded 72 g (80%) of an E- and Z-mixture. The first fraction, b.p. 127-129 (1.5 g), was the Z isomer. The second fraction, b.p. 129-134° (66.3 g) was a mixture of E and Z isomers, ir (liquid film): 1698 (C=O), 1595 and 1587 (C=C), 1580 (C=C ar. str.) 644 cm^{-1} (C-S str.); nmr: δ 7.45 (m, 5H), 5.9 (m, 1H) CH=C (Z isomer), 5.3 (m, 1H) CH=C (E isomer) 4.15 (9, J = 7 Hz, 2H) CH_3CH_2O, 2.48 (d, J = 0.7 Hz, 3H) $CH_3C=C$ (Z isomer), 1.8 (d, J = 0.7 Hz, 3H) $CH_3C=C$ (E isomer), 1.2 (t, J = 7 Hz, 3H) CH_3CH_2O; mass spectrum m/e: 222 (72), 177 (51), 149 (100), 134 (19), 110 (36), 85 (32). The third fraction, b.p. 134-136° (4.2 g) was the E isomer.

Ethyl β-n-butylthiocrotonate - n-Butylthiol (38 g, 0.42 mol) was added to ethanol (200 ml) containing an equivalent of sodium ethoxide (from 9.8 g Na, 0.42 mol) at 0°C. To this solution

ethyl β-chlorocrotonate (62.95 g, 0.424 mol) was added dropwise over a period of 15 min at 0°C. The reaction was left stirring overnight at room temperature during which time a white precipitate formed. The mixture was poured into ice cold water (4 l) and extracted with ether (4 x 200 ml). The combined ether extracts were reduced in volume and dried ($MgSO_4$). Ether was removed by distillation at atmospheric pressure and the residue was fractionally distilled through an 8 cm Vigreux column to afford 73 g (86%) of the E- and Z-isomers. The first fraction (3.2 g), distilling at 99-102°, was the Z isomer. The second fraction (68.2 g), distilling at 102-118, was the mixture of E and Z isomers; ir (liquid film): 1710 (C=O), 1600 (C=C); nmr: δ 5.75 and 5.48 (br, s, 1H) CH=C (E and Z), 4.12 (q, J = 7Hz, 2H) CH_3CH_2O, 2.72 (br, t, 2H) S-CH_2CH_2, 2.38 and 2.2 (d, J = 0.5 Hz, 3H) CH_3-C=C (E and Z), 1.85 to 1.4 (m, 4H) CH_2CH_2, 1.3 (t, J = 7 Hz, 3H) CH_3CH_2O, 0.9 (br t, 3H) $CH_3(CH_2)_3S$; mass spectrum m/e: 202 (92), 177 (10), 169 (13), 157 (100), 156 (85), 146 (94), 127 (41), 125 (26), 124 (40), 101 (71), 100 (98), 85 (26). The third fraction (5.8 g) distilling at 118-120°, was the E isomer.

Preparation of ethyl γ-phenyl(n-butyl)thiocrotonate from ethyl acetoacetate. A mixture of ethyl acetoacetate (6.5 g, 0.05 mol), benzenethiol (5.4 g, 0.05 mol) and p-toluenesulfonic acid monohydrate (0.5 g) was refluxed in benzene (50 ml) over a period of 10 hours with azeotropic removal of water. At the end of this period the reaction mixture was quenched with cold saturated potassium carbonate

solution (50 ml), then extracted with ether (3 x 25 ml). The organic layer was washed with water and brine and dried (Na_2SO_4). Removal of solvent (rotatory evaporator) and fractional distillation afforded 6.9 g (63%) of ethyl β-phenylthiocrotonate (E and Z mixture), b.p. 127-136°/1.5 mm, possessing ir, nmr and mass spectra identical with a sample prepared by Vernon's route.[90] The residue, phenylthioacetal of ethyl acetoacetate, was purified by evaporative distillation (110°/0.02 mm); nmr, δ 7.8 to 7.4 (m, 10H), 4.18 (9, 2H) CH_3CH_2O, 2.8 (s, 2H) CH_2CO_2Et, 1.65 (s, 3H) $CH_3C(S\phi)_2$, 1.25 (t, 3H) CH_3CH_2O; mass spectrum m/e: 332 (0.6), 287 (1.9), 260 (3.2), 223 (64), 177 (32), 151 (100), 129 (62).

Ethyl β-n-butylthiocrotonate was prepared as described above from ethyl acetoacetate (6.5 g, 0.05 mol) and n-butylthiol (4.51 g, 0.05 mol) to afford 6 g (59%) of ethyl β-n-butylthiocrotonate, as a mixture of E and Z isomers with identical properties (b.p., nmr, ir) to material prepared by Vernon's route.

Preparation of ethyl 3-oxopentanoate[91] - To a dry 100 ml flask equipped with a magnetic stirring bar, thermometer, pressure equalizing addition funnel, and nitrogen inlet, was added sodium hydride (2.16 g, 50% mineral oil, 44 mmol). The flask was flushed with nitrogen, cooled in an ice bath and charged with 35 cc of dry THF. Then ethyl acetoacetate (4.64 g, 40 mmol) was added dropwise and the colorless solution was stirred for 10 min at 0°. To this solution was added, dropwise, a solution of n-butyllithium (17.3 ml,

2.43 m, 42 mmol) in hexane. The resulting yellow solution of the dianion was stirred at 0° for an additional 10 min. Methyl iodide (6.25 g, 44 mmol) in THF (10 ml) was added dropwise (10 min) at 0° and the mixture was allowed to warm to room temperature with stirring (20 min). Then a mixture of 8 ml of conc. HCl in 20 ml of water and 50 ml of ether was added. The aqueous layer was extracted with ether (2 x 20 ml). The organic extracts were combined, washed with water until neutral, and dried ($MgSO_4$). Evaporation of the solvent and fractional distillation produced 3.2 g (75%) of ethyl 3-oxopentanoate b.p. 62-64/3 mn (lit.[136] 75-78°/9 mm), ir ($CHCl_3$) 1740 (C=O), 1715 cm^{-1} (C=O); nmr: δ 4.22 (9, J - 7 Hz, 2H) CH_3CH_2O, 3.48 (s, 2H) CH_2-CO_2Et, 2.59 (q, J = 7.2 Hz, 2H) $CH_2CH_2C{=}O$, 1.3 (t, J = 7 Hz, 3H) CH_3CH_2O, 1.08 (t, J = 7.2 Hz, 3H) $CH_3CH_2C{=}O$; mass spectrum m/e: 144.0791 (Calcd. for $C_7H_{12}O_3$: 144.0706), 144 (24), 125 (28), 99 (18), 87 (36), 69 (20), 57 (100), 43 (40).

Reaction of ethyl 3-oxopentanoate with benzenethiol in the presence of P-TSA. A mixture of ethyl 3-oxopentanoate (3.08 g, 22.4 mmol), benzenethiol (2.35 g, 2.16 ml, 22 mmol), and p-toluenesulfonic acid monohydrate (0.5 g) was refluxed in benzene (50 ml) for 10 hr with azeotropic removal of water. Then 50 ml of a cold saturated potassium carbonate solution was added and the aqueous layer was extracted with ether (3 x 25 ml). The organic extracts were combined, washed with water, then brine, and finally dried over Na_2SO_4. The solvents were removed (rotatory evaporator) and the crude residue was distilled through a 2 cm Vigreux column attached to a short path distillation

apparatus to afford 3.1 g (62%) of a mixture (50:50 by nmr) of ethyl 3-phenylthio-2-pentanoate and ethyl 3-phenylthio-3-pentanoate, b.p. 105-125°/0.02, ir (liquid film): 1745 (C=O, β,γ-isomer), 1715 (C=O, α,β-isomer), 1600 cm^{-1} (C=C); nmr: δ 7.3 to 7.25 (m, 5H) aromatic protons, 6.15 (m, 1H) $CH_3CH{=}C$, 5.2 (s, 1H) $C{=}CH\text{-}CO_2Et$, 4.1 (q, 4H) CH_3CH_2O, 3.25 (m, 2H) CH_2CO_2Et, 2.9 (q, J = 7.5 Hz, 2H) $CH_3CH_2C{=}CH$, 8.1 (d of t, 3H, J_{45} = 5 Hz, J_{25} = 0.5 Hz) $CH_3CH{=}C\text{-}CH_2$, 1.3 (t, J = 7 Hz, 3H) CH_3CH_2O, 1.08 (t, J = 7.2 Hz, 3H) $CH_3CH_2C{=}CH$; mass spectrum m/e: 236.0879 (Calcd. for $C_{13}H_{16}O_2S$: 236.0871) 236 (100), 218 (11), 191 (110), 190 (40), 163 (40), 162 (22), 135 (27), 136 (39), 110 (60), 109 (35), 99 (39).

Synthesis of Ethyl-5-phenyl-2-pentanoate[96] - To a cold (-78°) solution of allene (ca 4.5 ml, 75 mmol) in ether (35 ml) a solution of n-butyllithium (Foote, 34.5 ml, 1.52 M, 52.5 mmol) was added over a period of 30 min. The mixture was slowly allowed to warm to -15° and then stirred for 15 minutes at this temperature. A solution of benzyl chloride (1.9 g, 15 mmol) in ether (10 ml) was then added at -15° over a period of 15 minutes. The mixture was warmed (30 min) to room temperature, and one hour later was cooled to -78°. Freshly distilled ethyl chloroformate (40 g, 0.37 mmol) was added dropwise (30 min) and the temperature was gradually allowed to increase to 25° (3 hours). The reaction mixture was poured into ice-water, saturated with sodium chloride, and extracted with ether. The organic extracts were combined and washed with saturated ammonium chloride solution, brine, then dried over Na_2SO_4. The solvent was

removed (rotatory evaporator) and the residue was distilled to provide 2.43 g (80%) of ethyl (5-phenyl-2-pentynoate (b.p. 118-119°/ 0.4 mn); n_D^{20} 1.5210; ir (thin film) 2240 (C≡C), 1715 (C=O), 755 and 705 (C_6H_5); nmr: δ 7.17 (s, 6H) C_6H_5, 4.08 (q, J = 7 Hz, 2H) -O-CH_2, 2.62 (m, 4H) CH_2CH_2, 1.18 (t, J = 7 Hz, 3H) CH_3; mass spectrum m/e: 202.1001 (Calcd. for $C_{13}H_{14}O_2$: 202.0994), 157 (12), 129 (37), 91 (100), 66 (17), 51 (10), 39 (9), 29 (12).

Reaction of ethyl 5-phenyl-2-pentynoate with sodium thiophenoxide. Benzenethiol (1.33 g, 0.011 mol) was added to ethanol (75 ml) containing an equivalent amount of sodium ethoxide (0.258 g Na, 11.2 mmol) at 0°. To this solution ethyl 5-phenyl-2-pentynoate (2.268 g, 11.2 mmol) was added dropwise over a period of 15 min at 0°C. The resulting mixture was left stirring overnight at room temperature, then poured into ice cold water (1.5 l). After extracting the mixture with ether (4 x 100 ml), the combined ether extracts were reduced in volume and dried ($MgSO_4$). Ether was then removed (rotatory evaporator) and the residue was distilled (bulb to bulb) at 118-120/0.015 mm to afford 2.6 g (88%) of a mixture of 5-phenyl-5-phenylthio-2-pentanoate and 5-phenyl-3-phenylthio-3-pentanoate; ir (liquid film): 1740 (C=O, β,γ-isomer), 1710 C=O, α,β-isomer), 1630 (C=C), 1200, 775 and 705 cm^{-1} (C_6H_5); mass spectrum m/e: 312 (4.4), 218 (19), 202 (36), 174 (43), 168 (32), 157 (34), 129 (100), 128 (64), 109 (30), 91 (39).

Reaction of ethyl β-phenylthiocrotonate with DIBAH in THF. To a 100 ml 3-necked flask equipped with a magnetic stirring bar, thermometer, condenser, pressure equalizing addition funnel and N_2 inlet was added THF (15 ml). The flask was cooled to 0° and DIBAH (Alfa, 6.4 g, 8 ml, 0.045 mol) was then added under N_2. To this solution ethyl β-phenylthiocrotonate (5 g, 0.0225 mol) in THF (10 ml) was added dropwise (15 min) at 0°. The reaction mixture was allowed to warm slowly to room temperature and kept stirring at this temperature for an additional 2 hours. After the mixture was cooled to -10°C, methanol (15 ml) was added dropwise (15 min) followed by 15 ml of cold water. When H_2 evolution ceased, the reaction mixture was poured into a saturated solution of potassium carbonate (50 ml), then extracted with ether (3 x 25 ml) and dried (Na_2SO_4). After removal of solvent (rotatory evaporator) the residue was distilled to provide 2.8 g (69%) of 3-phenylthio-2-butanol (mixture of the E and Z isomers) b.p. 111-122/0.3 mm, ir (liquid film): 3350 (OH), 1640 (C=C), 1000 (C-O st), 750 and 700 cm^{-1} (C_6H_5); nmr: δ 7.3 (m, 5H) C_6H_5, 6.1 to 5.55 (m, 1H) CH_3CH=C, 4.35 and 4.1 (br d, J = 7.5 Hz, 2H, E and Z isomer) C=CH-CH_2-OH, 2.35 (s, 1H) OH, 1.95 (br s, 3H) CH_3; mass spectrum m/e: 180 (55), 161 (16), 149 (51), 111 (30), 110 (100), 109 (36), 108 (28), 77 (30). Anal. calcd. for $C_{10}H_{12}OS$: C, 66.60; H, 6.66. Found: C, 66.78; H, 6.58.

Reaction of ethyl β-n-butylthiocrotonate with DIBAH in THF. Ethyl β-n-butylthiocrotonate (4.55 g, 0.022 mol) was reduced with DIBAH

(alfa, 6.4 g, 8 ml, 0.045 mol) as described above to afford 2.5 g (70%) of the E and Z isomers of 3-n-butylthio-2-butanol. An analytical sample was obtained by bulb to bulb distillation, 70°/ 0.02 mm, ir (liquid film): 3400, 1640, and 1000 cm^{-1}; nmr: δ 5.8 to 5.25 (m, 1H) CH=C, 4.16 (d, J = 7.5 Hz, 2H) $C=CH-CH_2-OH$ 2.9 to 2.65 (t, 2H) CH_2-S, 2.72 (1, 1H) OH, 1.95 (br s, 3H) CH_3, 1.78-1.34 (m, 4H) CH_2CH_2, 1.0 (t, 3H) $CH_3(CH_2)_3S$; mass spectrum m/e: 160 (34), 143 (6), 103 (100), 90 (7), 87 (11), 86 (10), 75 (14), 71 (16), 69 (10). Anal. Calcd. for $C_8H_{16}OS$: C, 59.94; H, 10.06; S, 20.00. Found: C, 60.15; H, 10.11; S, 20.05.

Reduction of ethyl β-phenylthiocrotonate with aluminum hydride in ether[102]. Aluminum chloride (0.895 g, 6.75 mmol) was added to a suspension of LAH (0.77 g, 20 mmol) in ether (15 ml) at 0° under N_2. Dissolution of aluminum chloride and precipitation of lithium chloride took place readily upon warming to room temperature. A solution of ethyl β-phenylthiocrotonate (3 g, 27 mmol) in — ml of ether was then added, and the reaction was stirred for 30 min at 0°, then for 2 hours at room temperature. At the end of this period the reaction mixture was quenched with ice cold saturated potassium carbonate solution (50 ml) and extracted with ether (3 x 20 ml). The combined extract was washed with water, brine and dried (Na_2SO_4). After evaporation of solvent, the residue was distilled to afford 1.95 g (80%) of 3-phenylthio-2-butanol, b.p. 108-123°, 10.3 mm (E and Z isomers), identical in all respects to the compound obtained by the reduction with DIBAH.

Reduction of ethyl β-phenylthiocrotonate with aluminum hydride in THF

Aluminum chloride (1.99 g, 13.5 mmol) was placed in a 250 ml 3-necked flask equipped with a magnetic stirring bar and N_2 inlet. The flask was stoppered with a septum cap, flushed with nitrogen and cooled (ca -28). Then THF (25 ml) was syringed into the flask portionwise (exothermic reaction) and the resulting solution was allowed to stir for 30 min at room temperature. A separate 3-necked flask (equipped with an addition funnel, magnetic stirring bar, condenser, thermometer and N_2 inlet) was charged with LAH (1.58 g, 40 mmol), cooled (-10°) and THF (10 ml) was added. To this suspension the preformed aluminum chloride solution was added and the reaction mixture was stirred for 15 min at 0°C. Then ethyl β-phenylthiocrotonate (6 g, 54 mmol) in THF (10 ml) was added dropwise (15 min) and the reaction temperature was kept between 0° to 10°. This mixture was allowed to slowly reach room temperature and was stirred for an additional 1.5 hours. At the end of this period the reaction was quenched with a saturated solution of potassium carbonate (400 ml) and extracted with ether (3 x 75 ml). The combined extract was washed with water, brine and dried (Na_2SO_4). Solvent was removed (rotatory evaporator) and the residue was distilled to afford 4.4 g (90%) of 3-phenylthio-2-butanol, b.p. 108-123/0.3 mm (E and Z isomers) identical in all respects to the compound obtained by the reduction with DIBAH.

Reduction of ethyl β-n-butylthiocrotonate with aluminum hydride in THF

In a similar manner, ethyl β-n-butylthiocrotonate (5.44 g, 26.5 mmol) was reduced with aluminum hydride in THF solution. The aluminum

hydride was made from aluminum chloride (1.99 g, 13.5 mmol) and LAH (1.58 g, 40 mmol) according to the procedure described above. This reduction afforded 4 g (94%) of 3-n-butylthio-2-butanol, identical in all respects to the alcohol obtained by the reduction of ethyl β-n-butylthiocrotonate with DIBAH.

Attempted conversion of 3-phenylthio-2-butanol to the corresponding halide via Meyers' method.[106] A stirred mixture of the allylic alcohol (0.6 g, 3.3 mmol) and s-collidine (0.425 g, 3.5 mmol) under nitrogen was treated with lithium chloride (0.14 g, 3.3 mmol) dissolved in dry DME (3 ml). The solution was cooled to 0°C and methanesulfonyl chloride (0.4 g, 3.5 mmol) in DME (5 ml) was added dropwise (15 min). Stirring was continued at 0° for 1.5 hr. At the end of this period the reaction mixture was poured over ice-water. The aqueous layer was extracted with cold ether-pentane (1:1) (3 x 10 ml) and the combined extract was washed with saturated copper nitrate solution (3 x 10 ml). The organic extract was dried (Na_2SO_4) and concentrated (rotatory evaporator) to afford a brown oil which exhibited no absorption at 1255 cm^{-1} in the infrared spectrum, ir (liquid film): 3075, 3015, 1680, 1630, 1230, 925 and 975 cm^{-1}.

Reaction of 3-phenylthio-2-butanol with tri-n-butylphosphine in carbon tetrachloride. To a magnetically-stirred solution of 3-phenylthio-2-butanol (3.8 g, 20.3 mmol) in carbon tetrachloride under nitrogen was added tri-n-butylphosphine (5.1 g, 6.3 ml, 25 mmol)

dropwise (15 min) at 0°C. No apparent exothermic reaction took place at this temperature. The reaction mixture was slowly warmed to 10° (15 min) at which point a mild exothermic reaction took place (temperature rose to 20°). The mixture was stirred for an additional 15 min, then concentrated (rotatory evaporator). The residue was triturated with pentane and cooled to -78°. The resulting solid was filtered and washed with cold pentane. The combined pentane washings were washed with water, then brine and dried (Na_2SO_4). Removal of the solvent resulted in a brown oil which exhibited the following ir absorption: (liquid film) 3080, 2980, 2900, 1635, 1590, 1255, 1165, 975, 910, 795, 775, 700 cm^{-1} (mixture of the α- and γ-phenylthiocrotylchloride).

Preparation of γ-phenylthiocrotyl chloride via Young's method.[110] A 100 ml 3-necked flask equipped with thermometer, addition funnel, magnetic stirring bar, Dry Ice condenser, and nitrogen inlet was charged with 3-phenylthio-2-butanol (2.88 g, 18 mmol) and tri-n-butylamine (3.2 g, 18 mmol) in 20 ml of ether. The flask was cooled to -20°C and thionyl chloride (1.2 ml, 18 mmol) in ether (20 ml) was added dropwise over a period of 1.5 hr at -10 to -20°C. During the addition of $SOCl_2$ a slow stream of N_2 was used to sweep out SO_2 and HCl. The reaction mixture was kept for an additional 1 hr at -5° to 0°, then poured into ice-cold water (300 ml), and extracted with pentane (3 x 60 ml). The combined pentane extract was washed with brine and dried (Na_2SO_4). Removal of solvent left a pale yellow liquid (3.05 g, 85%) which was used immediately in the alkylation

reaction without purification. ir (liquid film): 1530 (C=C), 1585, 1470, 1440, 1375, 1255 (γ,γ-dissubstituted allylic chloride)[121] 1180, 1090, 1060, 1023, 775, 700 cm^{-1}; nmr: δ 7.35 (m, 5H) C_6H_5, 5.98 to 5.38 (m, 1H) $C=CH-CH_2-Cl$, 4.4 and 4.05 (br d, 2H) $C=CH-CH_2-Cl$ (E and Z isomer), 1.85 (m, 3H) CH_3; mass spectrum m/e: 198 (36), 163 (100), 135 (46), 130 (36), 124 (24), 110 (45), 109 (38), 91 (19), 77 (24), 71 (23).

A sample of crude γ-phenylthiocrotyl chloride was subjected to bulb to bulb distillation, b.p. 72-78°/0.025 mn to afford a colorless liquid in about 30% which is tentatively identified as 2-phenylthio-1,3-butadiene. The nmr shows only aromatic and olefinic protons at δ 7.35 (m, 5H) C_6H_5, 6.68 and 6.35 (d, J = 10 Hz, 2H), 5.85 to 5.08 (m, 3H); mass spectrum m/e: 163 (83), 147 (23), 129 (46), 110 (67), 91 (15), 71 (100), 53 (86), 51 (49), 45 (36), 39 (40).

A sample of the crude γ-phenylthiochloride was chromatographed rapidly over neutral (Woelm) silica gel (activity III) using pentane and then pentane : methylene chloride (1:1 by volume) as eluant. Examination by infrared of the fractions collected from the column showed no absorption at 1255 cm^{-1} (instead carbonyl absorptions at 1715 cm^{-1} and 1685 cm^{-1} appeared which indicated isomerization and hydrolysis of the chloride).

Preparation of γ-n-butylthiocrotyl chloride. In a similar manner, γ-n-butylthiocrotyl chloride was prepared from 3-n-butylthio-2-butanol (4 g, 25 mmol), tri-n-butylamine (4.8 g, 26 mmol) and thionyl chloride (3.1 g, 1.85 ml, 26 mmol) in 40 ml of ether. This afforded

3.7 g (85%) of pale yellow oil which was used without purification in the alkylation reactions; ir (liquid film): 2980, 2925, 2785, 1635 (C=C), 1465, 1440, 1380, 1255 (γ,γ-disubstituted allylic chloride),[121] 1175, 1090, 1060, 1030 cm^{-1}; nmr: δ 5.85 to 5 (m, 1H) CH=C, 4.28 and 4.05 (d, J = 8 Hz, 1H) $CH-CH_2-Cl$, 2.65 (br t, 2H) CH_2S, 1.95 and 1.68 (br s, 3H) CH_3, 1.68 to 1.07 (m, 4H) CH_2CH_2, 0.85 (t, 3H) $CH_3(CH_2)_3S$; glc mass spectrum, m/e: 142 (21, P-HCl), 127 (6), 113 (7), 99 (14), 86 (100), 85 (35), 71 (47), 59 (23), 53 (54), 45 (50), 41 (64), 39 (41).

Alkylation of 2,6-dimethylcyclohexanone with γ-phenylthiocrotyl chloride in DME. A 100 ml 3-necked flask equipped with addition funnel, magnetic stirring bar, thermometer, and N_2 inlet was charged with methyllithium (4.64 ml, 1.8 m, 8.35 mmol) in ether. The solvent was removed under reduced pressure and replaced by DME (10 ml). 2,2-Bipyridyl (10 mg) was added (resulting in a purple solution) and the solution was cooled to -50°. Diisopropylamine (0.844 g, 8.35 mmol) in DME (5 ml) was added dropwise and with stirring over 5 min. The resulting reddish-purple solution was stirred at -20° for 5 min and then 10 ml of a solution containing 2,6-dimethylcyclohexanone (1 g, 7.94 mmol) was added dropwise with stirring over 30 min, during which time the temperature of the solution was kept between -20° to 0°C. The resulting reddish-purple (indicating the presence of excess lithium diisopropylamide) solution was warmed to 30° and then γ-phenylthiocrotyl chloride (13 mmol) in DME (10 ml) was added rapidly (15 sec). The resulting mixture was warmed to

40° and stirred for 1 hr, then left overnight at room temperature. At the end of this period the reaction mixture was poured into 50 ml of cold saturated sodium hydrogen carbonate solution and extracted with pentane (3 x 15 ml). The pentane extract was washed successively with aqueous 5% HCl and aqueous sodium hydrogen carbonate solution, dried and concentrated. The residue was chromatographed over neutral (Woelm) silica gel, activity III, using skell B, then skelly B methylene chloride (2:1 by volume) as eluants. This yielded 0.3 g (30%) of starting material, 2,6-dimethylcyclohexanone, followed by 2-phenylthio-1,3-butadiene (decomposition product of the starting halide) and finally the product, 2,6-dimethyl-6-[γ-phenylthiocrotyl] cyclohexanone 1.4 g (65%), as a yellowish oil, ir (liquid film): 1715 (C=O), 1635 (C=C), 755 and 705 cm^{-1} (C_6H_5); nmr: δ 7.3 (m, 5H) C_6H_5, 5.84-5.62 (m, 1H) CH_3-C=CH-CH_2, 2.8-2.5 (m, 1H), 2.5 to 2.27 (br, d, J = 7 Hz, 2H) CH_3-C=CH-CH_2, 1.93 (br, s, 3H) CH_3-C=CH-CH_2, 1.9 to 1.6 (m, 6H) methylene protons, 1.15 to 1.07 and 1.07 to 1.00 (d, J = 6.5 Hz, 3H) CH_3, 0.95 (s, 3H) CH_3; mass spectrum m/e: 288 (18), 196 (85), 163 (100), 135 (25), 130 (18), 126 (24), 110 (35), 95 (16), 69 (17), 55 (24). Anal. Calcd. for $C_{18}H_{24}SO$: C, 74.95; H, 8.38; S, 11.11. Found: C, 74.84; H, 8.49; S, 10.78.

Alkylation of 2,6-dimethylcyclohexanone with γ-phenylthiocrotyl chloride in the presence of lithium iodide. To the solution of the lithium enolate of 2,6-dimethylcyclohexanone (1.51 g, 12 mmol) in DME (20 ml) at 0° (prepared according to the above procedure using 12.6 mmol of methyllithium and 12.6 mmol of diisopropylamine),

lithium iodide (2.16 g, 16 mmol) was added under nitrogen and the flask was wrapped with aluminum foil. This was followed by rapid addition of the halide (ca 16 mmol) in DME (10 ml). The resulting mixture was stirred for 30 min (during which time the temperature rose to 25°), then worked up as described above. After removal of the solvents, the concentrate was shown to contain three components by glc analysis (column A, temperature programming 90-260°, program rate 15°/min). By comparison with authentic samples (prepared previously) the components were identified (in order of elution) as 2,6-dimethylcyclohexanone (8%), 2-phenylthio-1,3-butadiene (not estimated) and the desired product, 2,6-dimethyl-6-[γ-phenylthiocrotyl]cyclohexanone (85%). Chromatography as before yielded 2.7 g (80%) of the monoalkylated product.

Purification by carbon chromatography. Carbon chromatography was effected on Barnebey-Cheney AU-4 carbon which was refluxed with 1N HCl for several hours, washed with water and refluxed with 1N NaOH. The carbon was then washed with water until the filtrate was neutral, followed by methanol, chloroform, and methylene chloride, and allowed to air dry. In contrast to "ordinary" type chromatography, the eluting solvents were used in decreasing order of polarity. For example: 1 g of crude mixture containing (by glc analysis) 2,6-dimethylcyclohexanone (8%), the alkylating agent (not estimated) and 2,6-dimethyl-6-[γ-phenylthiocrotyl]cyclohexanone (85%) was applied to a carbon column (35 g, 2.2 x 28 cm) packed in methanol. The column was eluted with 150 ml of methanol followed by 500 ml

of acetone which removed the first two components. The monoalkylated product was eluted with 500 ml acetone : ethyl acetate (1:1) followed by 300 ml ethyl acetate. This afforded 0.72 g of the alkylated product. The column was then reconditioned by washing with benzene followed by chloroform and finally by methanol.

Reaction of potassium enolates of 2,6-dimethylcyclohexanone with γ-phenylthiocrotyl chloride. Potassium hydride (Alfa, 35% in oil, 1.6 g, 14 mmol) was placed in a flask equipped with a magnetic stirring bar, condenser, and injection part capped with a rubber sleeve stopper. The apparatus was purged with nitrogen and connected through a trap to an azotometer. The KH was washed with dry pentane (3 x 10 ml) and dry THF was added (12 ml). 2,6-Dimethylcyclohexanone (1.51 g, 12 mmol) in THF (10 ml) was added with stirring at room temperature. Hydrogen evolution was quantitative in 12 min. The enolate solution was cooled to 0° and γ-phenylthiocrotyl chloride (ca 16 mmol) in THF (8 ml) was added and the reaction mixture was allowed to warm to room temperature. Aliquots were taken at 30 min, 2 hr and 10 hr, and quenched with ammonium chloride solution. After work-up they were subjected to glc analysis, which indicated a complex mixture of products of which the monoalkylated ketone was formed in 45% yield.

Preparation of 2,6-dimethyl-6-[γ-n-butylthiocrotyl]cyclohexanone. To the solution of the lithium enolate of 2,6-dimethylcyclohexanone (4.15 g, 33 mmol) in DME (50 ml) at -2°C, lithium iodide (5.4 g,

45 mmol) was added under nitrogen and the flask was wrapped with aluminum foil. This was followed by rapid addition of freshly prepared γ-n-butylthiocrotyl chloride (ca 40 mmol) in DME (10 ml).[a] The resulting mixture was stirred for 40 min (during which time the temperature rose to 25°), then poured into 100 ml of cold saturated sodium hydrogen carbonate solution and extracted with pentane (3 x 25 ml). The pentane extract was washed successively with aqueous 3% HCl, aqueous sodium hydrogen carbonate solution, then dried ($MgSO_4$) and concentrated. The residue was purified by carbon column chromatography using methanol and methanol-acetone (1:1) as the eluting solvents. This afforded 7.0 g (75%) of 2,6-dimethyl-6-[γ-phenylthiocrotyl]cyclohexanone, ir (liquid film): 1715 (C=O), 1630 cm^{-1} (C=C); nmr: δ 5.78 to 5.05 (m, 1H) vinyl protons, 2.65 (br, t, 2H) CH_2-S, 2.0 (m, 3H) $\underline{CH_3}$-C=CH-CH_2, 1.9 to 1.28 (m, 6H) methylene protons, 1.05 to 0.95 (m, 9H) $\underline{CH_3}C\underline{H_2}$, $\underline{CH_3}$, $CH_3\underline{CH}$; mass spectrum m/e: 268.4281 (Calcd. for $C_{16}H_{28}SO$: 268.4287), 268 (2), 179 (4), 144 (12), 143 (100), 110 (6), 100 (11), 88 (24). Anal. Calcd. for $C_{16}H_{28}SO$: C, 71.58; H, 10.51; S, 11.94. Found: C, 71.78; H, 10.74; S, 12.17.

Preparation of 6-methyl-2-[γ-phenylthiocrotyl]cyclohexanone. This compound was prepared as above from 2-methylcyclohexanone (1.57 g, 14 mmol) and γ-phenylthiocrotyl chloride (ca 17 mmol) in the presence

---

a. A latter modification utilized simply a concentrated solution of the halide in pentane-ether (10 ml) instead of replacing the solvents with DME. This gave consistenly higher yields.

of lithium iodide (1.7 g, 17 mmol). The reaction was carried out in DME (35 ml) for 30 min. Glc analysis (column A, temperature programming 90°-260°, program rate 15°/min) indicated an 83-85% yield of 6-methyl-2-[γ-phenylthiocrotyl]cyclohexanone. Chromatography as before yielded 2.88 g (75%), ir (liquid film) 1715 (C=O), 1640 (C=C), 750 and 700 cm^{-1} (C_6H_5); nmr (100 mHz, $CDCl_3$): δ 7.25 (s, 5H) C_6H_5, 5.92 to 5.64 (m, 1H) CH_3-C=CH-CH_2, 2.7 to 1.4 (m, 10H) $(CH_2)_3$, CH-CH_3, C=CH-CH_2-CH, 1.85 (b, s, 3H) CH_3-C=CH, 1.15 to 1.07 and 1.07 to 1.00 (d, J = 6.5 Hz, 3H) CH-CH_3. Mass spectrum m/e: 274 (98), 270 (15), 165 (100), 163 (87), 147 (26), 135 (37), 130 (35), 110 (24), 95 (16), 91 (14), 81 (32). Anal. Calcd. for $C_{17}H_{22}SO$: C, 74.40; H, 8.08; S, 11.68. Found: C, 74.36; H, 8.35; S, 11.93.

Preparation of 6-methyl-2-[γ-n-butylthiocrotyl]cyclohexanone. This compound was prepared as above from 2-methylcyclohexanone (1.347 g, 12 mmol) and γ-n-butylthiocrotyl chloride (ca. 14 mmol) in the presence of lithium iodide (1.1 g, 17 mmol) in DME (30 ml) for 45 min at -2° to 25°. Glc analysis (Column A, temperature programming 90-260°C, program rate 15°/min) indicated an 84% yield of 6-methyl-2-[γ-n-butylthiocrotyl]cyclohexanone. Chromatography as before yielded 2.2 g (72%), ir (liquid film): 1715 (C=O), 1630 cm^{-1} (C=C); nmr: δ 5.78 to 5.1 (m, 1H) CH_3-C=CH-CH_2, 2.65 (br, t, 2H) CH_2-S, 2.0 (br, s, 3H) CH_3-C=CH-CH_2, 2.8 to 0.9 (m, 13H); mass spectrum m/e: 254 (15), 236 (27), 197 (18), 165 (30), 143 (100), 148 (57), 125 (15), 110 (12), 91 (22). Anal. Calcd. for $C_{15}H_{26}SO$: C, 70.80; H, 10.30; S, 12.60. Found: C, 70.36; H, 9.99; S, 12.44.

Preparation of 2-methyl-Δ^1-cyclohexenyl acetate[33] 66. A solution of acetic anhydride (115 g, 1.125 mol), 2-methylcyclohexanone (28 g, 0.25 mol) and aqueous 70% perchloric acid/0.17 ml, 1 mmol) in 300 ml of carbon tetrachloride was stirred at 25° for 3 hr and then poured into a cold (0-5°) mixture of 200 ml of pentane and 200 ml of saturated aqueous sodium bicarbonate. After excess solid sodium bicarbonate had been added to neutralize all the acetic acid formed, the pentane layer was separated and the aqueous phase was extracted with pentane. The combined pentane solutions were dried, concentrated and distilled to afford 35 g (90%) of enol acetate 66, b.p. 81-86°/18 mm, n_D^{25} 1.4570 (lit.[30] n_D^{25} 1.4562-1.4572); ir (liquid film) 1750 and 1700 cm^{-1}; nmr: δ 2.03 (s, 3H) $CH_3C{=}O$, 1.44 [m, (br, s), 3H] $CH_3CH{=}CH_2$.

Preparation of 2-methyl-2-[γ-phenylthiocrotyl]cyclohexanone. Methyllithium (43 mmol, obtained by concentrating an ether solution under reduced pressure) and 2,2-bipyridyl (10 mg) were dissolved in DME (25 ml) and the resulting purple solution was cooled to 0°. While the temperature of the solution was kept at 0-10°, a solution of enol acetate 66 (3.24 g, 21 mmol) in DME (10 ml) was added dropwise with stirring over 35 min. The resulting red-orange solution (indicating excess of methyllithium) was cooled to 2° and lithium iodide (3.24 g, 30 mmol) was added. This was followed by a solution of γ-phenylthiocrotyl chloride (ca 30 mmol) in ether-pentane (5 ml). The reaction mixture was stirred in the dark (the bath was removed and the flask was wrapped with aluminum foil) for 40 min (during

which the temperature rose to 25°) and then poured into 100 ml of cold saturated, aqueous sodium bicarbonate solution and extracted with pentane. The pentane extract was dried and concentrated. The residue was chromatographed on a carbon column to yield 5.8 g (74%) of 2-methyl-2-[γ-phenylthiocrotyl]cyclohexanone, ir (liquid film): 1715 (C=O), 1640 (C=C), 755 and 705 cm^{-1} (C_6H_5): nmr (100 mHz, $CDCl_3$): δ 7.3 (m, 5H) C_6H_5, 5.84 to 5.62 (m, 1H) CH_3-C=CH-CH_2, 2.5 to 2.27 (br, d, 2H) CH-CH_2, 1.97 (br, s, 3H) CH_3-C=CH, 1.9 to 1.6 (m, 8H) $(CH_2)_4$, 1.10 and 1.08 (s, 3H) CH_3; mass spectrum m/e: 274 (40), 770 (11), 198 (51), 164 (30), 163 (100), 135 (97), 130 (28), 102 (22), 110 (88), 91 (35). Anal. Calcd. for $C_{17}H_{22}SO$: C, 74.40; H, 8.08; S, 11.68. Found: C, 74.69; H, 7.99; S, 11.38.

Preparation of 2-[γ-phenylthiocrotyl]cyclohexanone. To a solution of the lithium enolate of cyclohexanone (1.37 g, 14 mmol) in DME (25 ml) at 0°, lithium iodide (1.75 g, 16 mmol) was added under nitrogen, this was followed by a solution of γ-phenylthiocrotyl chloride (ca 16 mmol) in ether-pentane (5 ml). The reaction mixture was stirred in the dark for 35 min during which the temperature reached 25°C. Work-up, as described for the 2,6-dimethylcyclohexanone case, followed by chromatography on a carbon column afforded 2.73 (75%) of 2-[γ-phenylthiocrotyl]cyclohexanone, ir (liquid film) 1715 (C=O), 1630 (C=C), 750 and 700 cm^{-1} (C_6H_5); nmr: δ 7.3 (m, 5H) C_6H_5, 6.05 to 6.4 (m, 1H) CH_3C=CH-CH_2, 2.7 to 1.5 (m, 14H); mass spectrum m/e: 260 (7), 198 (20), 180 (15), 162 (70), 135 (89), 129 (59), 110 (100), 98 (40), 91 (31). Anal.

calcd. for $C_{16}H_{26}SO$: C, 73.79, H, 7.71; S, 12.31. Found: C, 73.74; H, 7.85; S, 12.44.

Preparation of 1-trimethylsiloxy-3-methylcyclohexene.[123] To a cooled (0°) slurry of copper (I) iodide (5.54 g, 30 mmol) in ether (30 ml) was added an ethereal solution of methyllithium (36.2 ml, 1.65 M, 60 mmol). After the addition was complete, 2-cyclohex none (2.7 g, 78 mmol) in ether (10 ml) was added, the resulting mixture was stirred for 15 min at 0°, and chlorotrimethylsilane (12 ml), triethylamine (15 ml) and HMPA (7 ml) were rapidly added. The mixture was then stirred at room temperature for 1 hr, after which time it was diluted with pentane (100 ml). The resulting mixture was washed successively with two 50 ml portions each of 5% HCl and 5% $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed at atmospheric pressure and the residue was distilled to yield 3.957 g (77%) of 1-trimethylsiloxy-3-methylcyclohexene; b.p. 49°/3 mm [lit.[130] 35°/1.4 mm]; ir (liquid film) 1660 cm^{-1} (enol ether); nmr: δ 4.63 (m, 1H) CH=C, 0.83 (d, 3H) CH_3, 0.17 (s, 9H) $SiMe_3$.

Preparation of 2-[γ-phenylthiocrotyl]-3-methylcyclohexanone. A mixture of the silyl enol ether (3.957 g, 21.4 mmol) and methyllithium-ether solution (13.3 ml, conc. 1.65 m, 22 mmol) was stirred at 25° for 30 min and then the ether was removed from the suspension of the lithium enolate. The residue was dissolved in DME (30 ml) and the solution was cooled to 0°. Lithium iodide (2.6 g, 20 mmol) was added, followed by γ-phenylthiocrotyl chloride (ca 25 mmol) in

ether-pentane solution (10 ml) and the reaction mixture was stirred in the dark for 45 min during which time the temperature was allowed to reach 25°. Then the reaction mixture was poured into 50 ml of cold saturated ammonium chloride solution and extracted with pentane (3 x 15 ml). The pentane extract was washed with water, then brine, and dried (Na_2SO_4), and concentrated. Glc analysis (Column A, temperature programming 90-268, program rate 15°/min) indicated a 90% yield of 2-[γ-phenylthiocrotyl]-3-methylcyclohexanone. Chromatography as before yielded 4.8 g (80%), ir (liquid film) 1715 (C=O), 1640 (C=C), 750 and 700 cm^{-1} (C_6H_5); nmr: δ 7.3 (m, 5H) C_6H_5, 6.04 to 5.68 (m, 1H), CH=C, 2.62 to 1.5 (m, 13H), 1.08 (d, J = 7 Hz, 3H) CH_3; mass spectrum m/e: 274.1381 (calcd. for $C_{17}H_{22}{}^{32}SO$: 274.1392) 274 (46), 264 (32), 248 (46), 234 (13), 209 (26), 204 (24), 165 (94), 163 (100), 147 (30), 135 (42), 110 (24), 109 (26), 95 (24), 81 (40). Anal. calcd. for $C_{17}H_{22}SO$: C, 74.40; H, 8.08; S, 11.68. Found: C, 74.17; H, 8.06; S, 11.88.

Reaction of 2,6-dimethyl-2-[γ-n-butylthiocrotyl]cyclohexanone with mercuric chloride. A mixture of mercuric chloride (0.75 g, 2.75 mmol) and 2,6-dimethyl-2-[6-n-butylthiocrotyl]cyclohexanone in 12 ml of aqueous acetonitrile (3 ml H_2O and 9 ml CH_3CN) was stirred at room temperature. The reaction was monitored by glc analysis which indicated complete consumption of the starting ketone after 40 hr. The mixture was filtered through alite with thorough ether washing. The filtrate was washed with aqueous sodium bicarbonate and then with brine, dried ($MgSO_4$) and concentrated (rotatory evaporation).

The resulting oil was passed through a short silica gel column (methylene chloride eluant) to remove mercuric salts, affording, after removal of solvent, 175 mg (95%) of 1,2,5-trimethylbicyclo-[3.3.1]non-2-en-9-one: ir (liquid film) 1715 cm^{-1} (C=O); nmr: δ 5.55 (m, 1H) HC=C, 1.61 (m, 3H) CH_3C=C, 1.03 and 0.95 (s, 3H) CH_3; mass spectrum m/e: 178 (2), 125 (5), 110 (3), 95 (8), 93 (8), 69 (12), 55 (27), 53 (16), 43 (100), 42 (15), 41 (51), 39 (43), 29 (33).

Reaction of 2,6-dimethyl-2-[γ-n-butylthiocrotyl]cyclohexanone with mercuric chloride in the presence of calcium carbonate. To the ketone (0.335 g, 1.25 x 10^{-3} mol) in 6 ml of 3:1 acetonitrile-water was added mercuric chloride (0.75 g, 2.75 mmol) in 8 ml of the same solvent followed by calcium carbonate (0.304 g, 3.3 mmol). The reaction was initially stirred for 6 hr at room temperature, then at reflux for an additional 6 hr. Glc analysis (column B temp 100°C) indicated only the presence of starting material.

Reaction of 2-methyl-2-[γ-phenylthiocrotyl]cyclohexanone with titanium tetrachloride in acetic acid. A dry three-necked flask (25 ml) equipped with thermometer, addition funnel, condenser, and a magnetic stirring bar was charged with glacial acetic acid (10 ml). Titanium tetrachloride (0.23 ml, δ = 1.689 g/cm^3, 2.1 mmol) was added and a yellow precipitate resulted. This mixture was stirred at room temperature for 5 min, then a solution of 2-methyl-2-[γ-phenylthiocrotyl]cyclohexanone (260 mg, 0.95 mmol) in glacial acetic

acid was added and the mixture stirred for 15 min at room temperature during which time the color of the mixture changed to olive green. At the end of this period water (0.07 g, 3.7 mmol) was added (which immediately caused a color change to deep red) and the mixture was stirred for an additional 30 min. The reaction mixture was poured into a cold saturated solution of potassium carbonate (25 ml), extracted with ether (3 x 15 ml) and dried (Na_2SO_4). After removal of the solvent at atmospheric pressure, the residue [containing 75-78% 10-methyl-1(9)-octal-2-one by glc (column E, 200)] was chromatographed over neutral (Woelm) silica gel, Activity III, using freshly distilled (from LAH) skelly B and methylene chloride (3:1 by volume) as eluants. This afforded 93 mg (63%) of 10-methyl-1(9)-octal-2-one, n_D^{25} 1.5227 (lit.[62] n_D^{25} 1.5230), ir (liquid film): 1680 (C=O), 1610 cm^{-1} (C=C); nmr: δ 5.5 (s, 1H) CH=C, 2.4 to 1.3 (m, 12H), 1.15 (s, 3H) CH_3; mass spectrum m/e: 164 (75), 136 (87), 122 (100), 121 (80), 107 (79), 93 (53), 91 (52), 79 (82), 41 (73), 40 (86).

Reaction of 2-methyl-2-[γ-phenylthiocrotyl]cyclohexanone with Tin tetrachloride. To a solution of tin tetrachloride (0.24 ml, d 2.226 g/ml, 2.1 mmol) in methylene chloride(10 ml) the above substrate (260 mg, 0.95 mmol) was added and the mixture was stirred at room temperature for 20 min. Then water (0.07 g, 3.7 mmol) was added and the resultant mixture was stirred at room temperature and monitored by glc analysis (column C, temp. 200°). A complex mixture of productswas formed, and the yield of enone, 10-methyl-1(9)-octal-2-one was less than 40%.

Hydrolysis-cyclization of 2-[γ-phenylthiocrotyl]cyclohexanone. Titanium tetrachloride (0.3 ml, 2.65 mmol) was added to glacial acetic acid (8 ml) and the resulting yellowish mixture was stirred at room temp. for 6 min. Then 2-[γ-phenylthiocrotyl]cyclohexanone (0.265 g, 1.06 mmol) in acetic acid (5 ml) was added and the brownish green solution was stirred for an additional 15 min at room temperature. Addition of water (0.0765 ml, 4.24 mmol) caused a color change to deep red. The resulting mixture was warmed to 55°C and kept stirring for 1 hr. At the end of this period the reaction mixture was poured into a cold saturated solution of potassium carbonate (25 ml), extracted with ether (3 x 15 ml) and dried (Na_2SO_4). After removal of solvent at atmospheric pressure, the residue [containing 77% 1(9)-octal-2-one by glc (column C, 200°)] was chromatographed over silica gel, Activity III, using Skelly B and methylene chloride (60:40) as eluants. First, 43 mg of a by-product was obtained: ir (liquid film) 1585 (conjugated double bond), 1460, 1440, 1260, 1110, 1080, 1040, 875, 810, 750 and 700 cm^{-1}; nmr: 2.7 (m, 5H) C_6H_5, 6.3 (br, s, 1H) CH=C, 2.7 to 1.1 (m, 11H). Then 103 mg (65%) of the product, 1(9)-octal-2-one was obtained. ir (liquid film): 1680 (C=O), 1610 cm^{-1} (C=C); nmr: δ 5.5 (s, 1H) CH=C, 2.4 to 1.3 (m, 13H); mass spectrum m/e: 150.1042 (calcd. for $C_{10}H_{14}O$: 150.1045) 150 (32), 122 (100), 108 (18), 107 (16), 94 (40), 93 (23), 91 (21), 79 (35), 77 (27), 67 (18), 66 (21), 56 (16).

Hydrolysis-cyclization of 2,6-dimethyl-2-[γ-n-butylthiocrotyl]-cyclohexanone. Titanium tetrachloride (2.8 ml, 2.62 mmol) was added to glacial acetic acid (80 ml) and the resulting yellowish mixture was stirred at room temperature for 6 min. The 2,6-dimethyl-2-[γ-n-butylthiocrotyl]cyclohexanone (2.7 g, 10.5 mmol) in acetic acid (20 ml) was added and the brownish solution was stirred for 20 min at room temperature. Water (0.725 ml, 42 mmol) was then added, which caused a color change to deep red. The reaction mixture was kept at room temperature under stirring for 4 hr and then quenched with a cold saturated solution of potassium carbonate (100 ml). The aqueous layer was extracted with ether (3 x 50 ml); the organic layer was washed with 20% potassium hydroxide solution, water, brine and dried (Na_2SO_4). After removal of solvent at atmospheric pressure, the residue [containing 73% 8,10-dimethyl-1(9)-octal-2-one by glc (column C, 22°)] was chromatographed over neutral silica gel (Woelm), Activity III using heptane-methylene chloride (60:40) as eluant to provide, in order of elution: vinyl sulfide 82, [0.785 g (30%), λ_{max}^{MeOH} 277 mμ (ε 9,150); ir (liquid film): 1590 cm^{-1} (conjugated double bond); nmr: δ 6.3 (br. s, 1H) CH=C, 2.9 to 0.8 (m, 25H); mass spectrum m/e: 250.1761 (calcd. for $C_{16}H_{26}{}^{32}S$: 250.1756)], then 1,2,5-trimethylbicyclo[3,3,1]non-2-en-9-one [(93 mg, 5%) which had identical nmr and ir spectra to the compound isolated previously] and finally, trans-8,10-dimethyl-1(9)-octal-2-one (1.18 g, 59%), ir (liquid film): 1680 (C=O) and 1610 cm^{-1} C=C); nmr: δ 5.77 (d, J = 2 Hz, 1H) CH=C, 1.28 (s, 3H) CH_3, 1.05 (d, J = 6.5 Hz, 3H)

CH_3; mass spectrum m/e: 178 (22), 163 (8), 150 (18), 136 (26), 135 (33), 119 (11), 107 (33), 105 (30), 93 (45), 91 (59), 79 (64), 77 (58), 67 (27), 65 (33), 55 (42), 53 (54), 51 (36), 41 (100), 39 (96), 29 (64).

Hydrolysis of 6-methyl-9-phenylthio-bicyclo[4.4.0]-1,9-decadiene, with titanium tetrachloride. Titanium tetrachloride (0.23 ml, 2.10 mmol) was added to glacial acetic acid (10 ml) and the resultant yellowish mixture was stirred at room temperature for 5 min. To this mixture the vinyl sulfide 82, (0.262 g, 1.05 mmol) in glacial acetic acid (4 ml) was added and the resulting brown solution was stirred for 15 min. Then water (0.075 ml, 420 mmol) was added (which immediately caused a color change to deep red) and the reaction mixture was kept at room temperature under stirring for 1 hr. Glc analysis (column E, 220°) indicated the formation of 75% of trans-8,10-dimethyl-1(9)-octal-2-one. Chromatography as before yielded 80 mg (60%) of the enone which had identical nmr and ir spectra to the compound isolated previously.

Hydrolysis-cyclization of 2-methyl-6-[γ-n-butylthiocrotyl]cyclohexanone. Using the same procedure as above, this compound (520 mg, 1.01 mmol) was treated with titanium tetrachloride (0.52 ml, 4.7 mmol) in glacial acetic acid (20 ml) for 15 min, then with water (0.138 ml, 4.7 mmol) in glacial acetic acid (2o ml) for 15 min, then with water (0.138 g, 4.6 mmol) and the reaction mixture was stirred for 4 hr at room temperature. Work-up as before afforded

73% trans-8-methyl-1(9)-octal-2-one as estimated by glc analysis (column D, 180°). Chromatography as before yielded 178 mg (59%) of the octalone, ir (liquid film): 1680 (C=O) and 1610 cm^{-1} (C=C); nmr: δ 5.72 (d, J = 3 Hz, 1H) CH=C, 1.12 (d, J = 6.5 Hz, 3H) CH_3; mass spectrum m/e: 164 (12), 135 (25), 121 (13), 109 (18), 108 (18), 94 (33), 93 (28), 91 (49), 80 (15), 79 (44), 77 (49), 65 (37), 56 (40), 51 (48), 43 (68), 41 (60), 39 (100), 29 (43).

REFERENCES

1. F.F. Blicke, Org. Reactions, 1, 303 (1942).
2. B. Reichert, "Die Mannich Reaktion", Springer Verlag, Berlin, 1959.
3. J.H. Brewster and E.L. Eliel, Org. Reactions, 7, 99 (1953).
4. J.C. Craig, M. Moyle, and L.F. Johnson, J. Org. Chem., 29, 410 (1964).
5. J.H. Burckhalter and R.C. Tuson, J. Amer. Chem. Soc., 70, 4184 (1948).
6. H.O. House, D.J. Reif, and R.L. Wasson, ibid., 79, 2490 (1957).
7. E.D. Bergmann, D. Ginsburg, and R. Pappo, Org. Reactions, 10, 179 (1959).
8. E.C. DuFew, F.J. McQuillin, and R. Robinson, J. Chem. Soc., 53 (1937).
9. F.J. McQuillin and R. Robinson, ibid., 1097 (1938).
10. J.W. Cornforth and R. Robinson, ibid., 1855 (1949).
11. L. Wilds and C.H. Shunk, J. Amer. Chem. Soc., 65, 469 (1943).
12. A.V. Logan, E.N. Marvell, R. LaPore, and D.C. Bush, ibid., 76, 4127 (1954).
13. J.A. Marshall, H. Faubl, and T.M. Warne, Jr., J. Org. Chem., 36, 178 (1971).
14. R.M. Coates and J.E. Shaw, Chem. Commun., 1, 47 (1968).
15. R.L. Hule and L.H. Zalkow, ibid., 20, 1249 (1968).
16. H.C. Odom and A.R. Pinder, ibid., 1, 26 (1969).
17. J.A. Marshall and D.J. Schaeffer, J. Org. Chem., 30, 3642 (1965) and references therein.
18. G. Stork and J.E. McMurry, J. Amer. Chem. Soc., 89, 5461, 5463, 5464 (1967) and references therein.
19. W.G. Dauben and J.W. McFarland, J. Amer. Chem. Soc., 82, 4245 (1960).
20. D. Caine and N.F. Tuller, J. Org. Chem., 34, 222 (1969).

21. S. Danishefsky and R. Cavanaugh, ibid., 92, 520 (1968).

22. R.B. Woodward and T. Singh, J. Amer. Chem. Soc., 72, 494 (1950).

23. S. Ramachandran and M.S. Newman, Org. Syn., 41, 38 (1961).

24. A.B. Mekler, S. Ramachandran, S. Swaminathan, and M.S. Newman, ibid., 41, 56 (1961).

25. M.S. Newman and A.B. McKler, J. Amer. Chem. Soc., 82, 4039 (1960).

26. M. Brown and W.S. Johnson, J. Org. Chem., 27, 4706 (1962).

27. N.B. Haynes and C.J. Timmons, J. Chem. Soc., 6, 224 (1966).

28. G.L. Buchanan, A.C.W. Curran, and R.T. Wall, Tetrahedron, 25, 5503 (1969) and references therein.

29. S.P. McManus, H.S. Bruner, H.D. Coble, and G. Choudhary, J. Chem. Soc. Chem. Comm., 253 (1974).

30. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, J. Amer. Chem. Soc., 85, 207 (1963).

31. G. Stork and P.F. Hudrlik, ibid., 90, 4462 (1968).

32. An extensive discussion and review of methods appears in H.O. House, "Modern Synthetic Reactions", 2nd ed., W.A. Benjamin, Menlo Park, Calif. 1972, chapter 9.

33. H.O. House, Martin Gall, and H.D. Olmstead, J. Org. Chem., 36, 2361 (1971), and references therein.

34. J. Hooz and J.N. Bridson, J. Amer. Chem. Soc., 95, 602 (1973).

35. J. Hooz and J.N. Bridson, Can. J. Chem., 50, 2387 (1972).

36. J. Hooz and S. Linke, J. Amer. Chem. Soc., 90, 5936, 6891 (1968);
J. Hooz and G.F. Morrison, Can. J. Chem., 48, 868 (1970);
J. Hooz and D.M. Gunn, Chem. Commun., 139 (1969);
J. Hooz and D.M. Gunn and H. Kono, Can. J. Chem., 49, 2371 (1971).

37. D.J. Pasto and P.W. Wojtkowski, Tetrahedron Lett., 31, 215 (1970).

38. J. Schrieber, H. Maag, N. Hashimoto and A. Eschenmoser, Angew. Chem., Int. Ed. Engl., 10, 330 (1971).

39. A. Suzuki, A. Arase, H. Matusmoto, M. Itoh, H.C. Brown, M.M. Rogić, and M.W. Rathke, J. Amer. Chem. Soc., 89, 5708 (1967); H.C. Brown, M.M. Rogić, M.W. Rathke, and G.W. Kabalka, ibid., 89, 5709 (1967); H.C. Brown, G.W. Kabalka, M.W. Rathke, and M.M. Rogić, ibid., 90,

4165 (1968); H.C. Brown, M.W. Rathke, G.W. Kabalka, and M.M. Rogić, ibid., 90, 4166 (1968); H.C. Brown and G.W. Kabalka, ibid., 92, 712, 714 (1970); H.C. Brown and E. Negishi, ibid., 93, 3777 (1971).

40. P.H. Hudrlik and A.M. Hudrlik, J. Org. Chem., 38, 4254 (1973).

41. G. Stork, G.A. Kraus, and G.A. Garcia, J. Org. Chem., 39, 3459 (1974).

42. T. Mukaiyama, K. Inomata, and M. Muraki, J. Amer. Chem. Soc., 95, 967 (1973) and references therein.

43. J. Hooz, J.N. Bridson, J.G. Calzada, H.C. Brown, M.M. Midland and A.B. Levy, J. Org. Chem., 38, 2574 (1973).

44. D.S. Matteson and R.W.H. Mah, J. Amer. Chem. Soc., 85, 2599 (1963).

45. G. Zweifel, J. Organometall. Chem., 9, 215 (1967).

46. H.C. Brown and P.A. Tierny, J. Inorg. Nucl. Chem., 9, 51 (1959).

47. D.J. Pasto and P. Bulasubramaniyan, J. Amer. Chem. Soc., 89, 295 (1967).

48. H.C. Brown, E.F. Knights, and R.A. Coleman, J. Amer. Chem. Soc., 91, 2144 (1969); H.C. Brown and M. Rogić, ibid., 91, 2146 (1969); H.C. Brown, M.M. Rogić, H. Numbu, and M.W. Rathke, ibid., 91, 2147 (1969).

49. J. Hooz and D.M. Gunn, Tet. Lett., 40, 3455 (1969).

50. A. Petter, M.G. Hutchings, K. Smith, and D.J. Williams, J. C.S. Perkin I, 145 (1975).

51. An extensive discussion appears in H.C. Brown, "Boranes in Organic Chemistry", 2nd ed., Cornell University Press, 1972, chapter 9.

52. G. Wilke and H. Mueller, Chem. Ber., 89, 444 (1956).

53. K. Ziegler, K. Schneider and J. Schneider, Ann. Chem. (Paris), 623, 9 (1959).

54. J. Hooz and D.M. Gunn, J. Amer. Chem. Soc., 91, 6195 (1969).

55. J. Schreiber, H. Maag, N. Hashimoto, and A. Eschenmoser, Angew. Chem., Int. Ed. Engl., 10, 330 (1971).

56. Nitrogen was purified either by passage through Fiesers solution (L. Fieser, J. Amer. Chem. Soc., 46, 2639 (1924)) or by passing it through sulfuric acid then sodium benzophenone ketyl in diglyme followed by a cooled (-78°) trap.

57. J.A. Moore and D.E. Read, Org. Syn., 41, 16 (1961).

58. J.N. Bridson and J. Hooz, Org. Syn., 53, 35 (1971) and references therein.

59. H.E. Smith and R.H. Eastman, J. Amer. Chem. Soc., 79, 5550 (1957).

60. M. Regitz, J. Rüter, and A. Liedhegena, Org. Syn., 51, 86 (1970).

61. J.W. Cornforth, Prog. Org. Chem., 31, 1 (1955).

62. J.A. Marshall and W.I. Fanta, J. Org. Chem., 29, 2501 (1964) and references therein.

63. F. Sondheimer and D. Rosenthal, J. Amer. Chem. Soc., 80, 3995 (1958).

64. R.E. Ireland, "Organic Synthesis", Prentice-Hall, Inc., Englewood Cliff, N.J., 1969, page 88.

65. R.B. Woodward, F. Sondheimer, D. Toub, K. Heusler, and W.M. Melamore, J. Amer. Chem. Soc., 74, 4223 (1952).

66. G.I. Fujimoto, J. Amer. Chem. Soc., 73, 1856 (1951).

67. R.B. Turner, ibid., 72, 579 (1950).

68. C.F.H. Allen, J.W. Gates, Jr., and J.A. Von Allan, Org. Syn., Coll. Vol. 3, 353 (1955).

69. G. Stork, S. Danishefsky, and M. Ohashi, J. Amer. Chem. Soc., 89, 5459 (1967).

70. J.E. Telschow and W. Rensch, J. Org. Chem., 40, 862 (1975).

71. G. Stork and B. Ganem, J. Amer. Chem. Soc., 95, 6152 (1973).

72. D.J. Peterson, J. Organometal. Chem., 9, 373 (1967).

73. G. Stork and J. Singh, J. Amer. Chem. Soc., 96, 6181 (1974).

74. R.K. Boeckman, Jr., ibid., 95, 6867 (1973).

75. R.K. Boeckman, Jr., ibid., 96, 6179 (1974).

76. C.H.Heathcock and E. Ellies, Tet. Let., 4995 (1971).

77. P.A. Zoretic, B. Branchaud and T. Maestrone, Org. Prep. and Proc., 7, 51 (1975); P.A. Zoretic, B. Branchaud and T. Maestrone, Tet. Lett., 527 (1975).

78. O. Wichterle, J. Prochazka, and Hoffmann, Collect. Czech. Chem. Commun., 13, 300 (1948).

79. S. Danishefsky, P. Cain, and A. Nagel, J. Amer. Chem. Soc., 97, 380 (1975) and references therein.

80. G. Stork, M.E. Jung, J. Amer. Chem. Soc., 96, 3582 (1974); G. Stork, M.E. Jung, E. Calvin and Y. Noel, ibid., 96, 3684 (1974).

81. P.L. Stotter, and K. A. Hill, ibid., 96, 6524 (1974); P.L. Stotter, and K.A. Hill, Tett. Lett., 1679 (1975).

82. T. Kumamoto, S. Kobayashi and T. Mukaiyama, Bull. Chem. Soc. Jpn., 45, 866 (1972); T. Mukaiyama, K. Kamino, S. Kobayashi, and M. Tukei, Bull. Chem. Soc. Jpn., 45, 3723 (1972).

83. E.J. Corey and J.T. Shulman, J. Org. Chem., 35, 777 (1970).

84. H.C. Brown, D.B. Bigley, S.K. Arora, N.M. Yoon, J. Amer. Chem. Soc., 92, 7161 (1970).

85. H. Kono and J. Hooz, Org. Syn., 55, 77 (1972).

86. G. Zweifel and H.C. Brown, J. Amer. Chem. Soc., 85, 2066 (1962).

87. C.A. Brown, J. Org. Chem., 30, 1324 (1974); C.A. Brown, ibid., 39, 3913 (1974).

88. B.S. Weiland and J.F. Arens, Rec. Trav. Chemin. Pays Bas., 79, 1293 (1960).

89. B.S. Kupin and A.A. Petrov, Zh. Org. Khim., 3, 975 (1967).

90. D.E. Jones, R.O. Morris, C.A. Vernon, and R.F.M. White, J. Chem. Soc., 2349 (1960).

91. S.N. Huckin and L. Weiler, J. Amer. Chem. Soc., 96, 1082 (1974).

92. T. Mukaiyama, H. Toda, and S. Kobayashi, Chem. Letter, 535 (1975).

93. M.G. Missakian, R. Ketcham, and A.R. Martin, J. Org. Chem., 39, 2010 (1974).

94. F. Theron and R. Vessière, Bull. Soc. Chim. (Fr), 7, 2994 (1968).

95. W.E. Truce and D.L. Goldhamer, J. Amer. Chem. Soc., 81, 5795 (1959).

96. J.G. Calzada, Ph.D. Thesis, University of Alberta (1974).

97. D.E. O'Connor and W.F. Lyness, J. Amer. Chem. Soc., 86, 3840 (1964).

98. G.H. Posner and D.J. Brunelle, J.C.S. Chem. Comm., 907 (1973).

99. A.E.G. Miller, J.B. Biss, and L.H. Schwartman, J. Org. Chem., 24, 627 (1959).

100. H.C. Brown and H. Suzuki, J. Amer. Chem. Soc., 89, 1933 (1967) and references therein.

101. K.E. Wilson, R.T. Seidner and S. Masamune, Chem. Comm., 213 (1970).

102. M.J. Jorgenson, Tet. Lett., 559 (1962).

103. N.M. Yoon and H.C. Brown, J. Amer. Chem. Soc., 90, 2927 (1968).

104. E.C. Ashby and B. Cooke, ibid., 90, 1625 (1968) and references therein.

105. A.E. Finholt, A.C. Bond, and H.I. Schlesinger, J. Amer. Chem. Soc., 69, 1199 (1947).

106. F.W. Collington and A.I. Meyers J. Org. Chem., 36, 3044 (1971).

107. I.M. Downie, J.B. Holmes, and J.B. Lee, Chem. Ind. (London), 900 (1966); J.B. Lee and J.J. Nolan, Can. J. Chem., 44, 1331 (1966).

108. J. Hooz and S.S. H. Gilani, Can. J. Chem., 46, 86 (1968).

109. I.M. Downie, J.B. Lee, and M.F.S. Matongh, Chem. Commun., 1350 (1968).

110. W.G. Young, F.F. Castro, Jr., and D.D. Branson, Jr., J. Amer. Chem. Soc., 82, 6163 (1960) and references therein.

111. G. Stork, P.A. Grieco, and M. Gregson, Tet. Lett., 18, 1393 (1969).

112. For a discussion of this mechanism see DeWolfe and Young, Chem. Rev., 56, 769 (1950).

113. G. Stork and W.N. White, J. Amer. Chem. Soc., 78, 4609 (1956).

114. H.O. House, L.J. Cuzba, M. Gall, and H.D. Olmstead, J. Org. Chem., 34, 2324 (1969).

115. B.M. Trost, K. Hiroi, and S. Kirrozumi, J. Amer. Chem. Soc., 97, 438 (1975).

116. R.M. Coates and L.O. Sandefur, J. Org. Chem., 39, 275 (1974).

117. R.K. Boeckman, Jr., ibid., 38, 4450 (1973).

118. P.A. Grieco and R. Finkelhor, ibid., 38, 2100 (1973).

119. G.H. Posner, J.J. Sterling, C.E. Whitten, C.M. Lenz, and D.J. Brunelle, J. Amer. Chem. Soc., 97, 107 (1975).

120. G. Stork and D.F. Hudrlik, J. Amer. Chem. Soc., 90, 4464 (1968).

121. D. Barnard, L. Bateman, A.J. Harding, H.P. Koch, N. Sheppard, and G.B.B. Sutherland, J. Chem. Soc., 915 (1950).

122. H.O. House, and W.F. Fischer, Jr., J. Org. Chem., 33, 949 (1968).

123. E.S. Binkley and C.H. Heathcock, J. Org. Chem., 40, 2156 (1975).

124. S. Julia, Bull. Soc. Chim. France, 21, 780 (1954).

125. E.J. Corey and B.W. Erickson, J. Amer. Chem. Soc., 36, 3555 (1971).

126. T. Mukaiyama, K. Narasaka, M. Furusato, J. Amer. Chem. Soc., 94, 8641 (1972).

127. E. Vedejs and P.L. Fuchs, J. Org. Chem., 36, 366 (1971).

128. T.L. Ho, H.C. Ho, and C.M. Wong, J.C.S. Chem. Comm., 791 (1972).

129. F.A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry", 2nd ed. Interscience Publisher, 1966, page 799.

130. J.R.M. Romero, C. Djerassi and G. Rosenkranz, J. Amer. Chem. Soc., 73, 1528 (1951).

131. T. Mukaiyama, K. Banno, and K. Narasaka, J. Amer. Chem. Soc., 96, 7503 (1974).

132. H.O. House, D.S. Crumrine, A.T. Teranishi and H.D. Olmstead, J. Amer. Chem. Soc., 95, 3310 (1973).

133. Unpublished results of Dr. L.M. Browne, University of Alberta, Postdoctoral Research Fellow.

134. Unpublished results of Dr. R.D. Mortimer, University of Alberta, Postdoctoral Research Fellow.

135. S.C. Watson and J.F. Eastham, J. Organometal. Chem., 9, 165 (1967).

136. "Dictionary of Organic Compounds", 4th Edition, Eyre and Spottiswoode, Ltd., London, 1965; Vol. 4, 2594.